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(54) Title: COMPOUNDS THAT INHIBIT INTERACTION BETWEEN SIGNAL-TRANSDUCING PROTEINS AND THE GLGF (PDZ/DHR) DOMAIN AND USES THEREOF (57) Abstract <p>This invention provides for a composition capable of inhibiting specific binding between a signal-transducing protein and a cytoplasmic protein. This invention also provides a method of identifying a compound capable of inhibiting specific binding between a signal-transducing protein and a cytoplasmic protein. This invention also provides a method of inhibiting the proliferation of cancer cells. This invention also provides a method of treating cancer with a composition in an amount effective to result in an amount in apoptosis of the cells. This invention also provides a method of inhibiting the proliferation of virally infected cells. This invention also provides for a method of treating a virally-infected subject with a composition in an amount effective to result in apoptosis of the cells. This invention also provides for pharmaceutical compositions.</p>		

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COMPOUNDS THAT INHIBIT INTERACTION BETWEEN SIGNAL-TRANSDUCING PROTEINS AND THE GLGF (PDZ/DHR) DOMAIN AND USES THEREOF

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The invention disclosed herein was made with Government support under Grant No. R01GM55147-01 from the National Institutes of Health of the United States Department of Health and Human Services. Accordingly, the U.S. Government has certain rights in this invention.

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BACKGROUND

Throughout this application, various publications are referenced by author and date. Full citations for these publications may be found listed alphabetically at the end of the specification immediately preceding Sequence Listing and the claims. The disclosures of these publications in their entireties are hereby incorporated by reference into this application in order to more fully describe the state of the art as known to those skilled therein as of the date of the invention described and claimed herein.

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Fas (APO-1/CD95) and its ligand have been identified as important signal-mediators of apoptosis (Itoh, et al. 1991) The structural organization of Fas (APO-1/CD95) has suggested that it is a member of the tumor necrosis factor receptor superfamily, which also includes the p75 nerve growth factor receptor (NGFR) (Johnson, et al. 1986), the T-cell-activation marker CD27 (Camerini, et al. 1991), the Hodgkin-lymphoma-associated antigen CD30 (Smith, et al. (1993), the human B cell antigen CD40 (Stamenkovic, et al. 1989), and T cell antigen OX40 (Mallett, et al. 1990). Genetic mutations of both Fas and its ligand have been associated with lymphoproliferative and autoimmune disorders in mice (Watanabe-Fukunaga, et al. 1992; Takahashi, et al. 1994).

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Furthermore, alterations of Fas expression level have been thought to lead to the induction of apoptosis in T-cells infected with human immunodeficiency virus (HIV) (Westendorp, et al. 1995).

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Several Fas-interacting signal transducing molecules, such as Fas-associated phosphatase-1 (FAP-1) (Figure 1) (Sato, et al. 1995) FADD/MORT1/CAP-1/CAP-2 (Chinnaiyan, et al. 1995; Boldin, et al. 1995; Kischkel, et al. 1995) and RIP (Stanger, et al. 1995), have been identified using yeast two-hybrid and biochemical approaches. All but FAP-1 associate with the functional cell death domain of Fas and overexpression of FADD/MORT1 or RIP induces apoptosis in cells transfected with these proteins. In contrast, FAP-1 is the only protein that associates with the negative regulatory domain (C-terminal 15 amino acids) (Ito, et al. 1993) of Fas and that inhibits Fas-induced apoptosis.

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FAP-1 (PTPN13) has several alternatively-spliced forms that are identical to PTP-BAS/hPTP1E/PTPL1, (Maekawa, et al. 1994; Banville, et al. 1994; Saras, et al. 1994) and contains a membrane-binding region similar to those found in the cytoskeleton-associated proteins, ezrin, (Gould et al. 1989) radixin (Funayama et al. 1991) moesin (Lankes, et al. 1991), neurofibromatosis type II gene product (NFII) (Rouleau, et al. 1993), and protein 4.1 (Conboy, et al. 1991), as well as in the PTPases PTPH1 (Yang, et al. 1991), PTP-MEG (Gu, et al. 1991), and PTPD1 (Vogel, et al. 1993). FAP-1 intriguingly contains six GLGF (PDZ/DHR) repeats that are thought to mediate intra- and inter-molecular interactions among protein domains. The third GLGF repeat of FAP-1 was first identified as a domain showing the specific interaction with the C-terminus of Fas receptor (Sato, et al. 1995). This suggests that the GLGF domain may play an important role in targeting proteins to the submembranous cytoskeleton

and/or in regulating biochemical activity. GLGF repeats have been previously found in guanylate kinases, as well as in the rat post-synaptic density protein (PSD-95) (Cho, et al. 1992), which is a homolog of the Drosophila tumor suppressor protein, lethal-(1)-disc-large-1 [*dlg-1*] (Woods, et al 1991; Kitamura, et al. 1994). These repeats may mediate homo- and hetero-dimerization, which could potentially influence PTPase activity, binding to Fas, and/or interactions of FAP-1 with other signal transduction proteins. Recently, it has also been reported that the different PDZ domains of proteins interact with the C-terminus of ion channels and other proteins (Figure 1) (TABLE 1) (Kornau, et al. 1995; Kim, et al. 1995; Matsumine, et al. 1996).

TABLE 1. Proteins that interact with PDZ domains.

Protein	C-terminal sequence	Associated protein	Reference
Fas (APO-1/CD95)	SLV	FAP-1	2
NMDA receptor NR2 subunit	SDV	PSD95	3
Shaker-type K+ channel	TDV	PSD95 & DLG	4
APC	TEV	DLG	5

SUMMARY OF THE INVENTION

This invention provides a composition capable of inhibiting specific binding between a signal-transducing protein and a cytoplasmic protein containing the amino acid sequence (G/S/A/E)-L-G-(F/I/L) (Sequence I.D. No.: 1). Further, the cytoplasmic protein may contain the amino acid sequence (K/R/Q)-X_n-(G/S/A/E)-L-G-(F/I/L) (Sequence I.D. No.: 2), wherein X represents any amino acid which is selected from the group comprising the twenty naturally occurring amino acids and n represents at least 2, but not more than 4. In a preferred embodiment, the amino acid sequence is SLGI (Sequence I.D. No.: 3). Further, the invention provides for a composition when the signal-transducing protein has at its carboxyl terminus the amino acid sequence (S/T)-X-(V/I/L) (Sequence I.D. No.: 4), wherein each - represents a peptide bond, each parenthesis encloses amino acids which are alternatives to one other, each slash within such parentheses separating the alternative amino acids, and the X represents any amino acid which is selected from the group comprising the twenty naturally occurring amino acids.

This invention also provides for a method of identifying a compound capable of inhibiting specific binding between a signal-transducing protein and a cytoplasmic protein containing the amino acid sequence (G/S/A/E)-L-G-(F/I/L). Further this invention provides for a method of identifying a compound capable of inhibiting specific binding between a signal-transducing protein having at its carboxyl terminus the amino acid sequence (S/T)-X-(V/L/I) and a cytoplasmic protein.

This invention also provides for a method inhibiting the proliferation of cancer cells, specifically, where the cancer cells are derived from organs comprising the

colon, liver, breast, ovary, testis, lung, stomach, spleen, kidney, prostate, uterus, skin, head, thymus and neck, or the cells are derived from either T-cells or B-cells.

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This invention also provides for a method of treating cancer in a subject in an amount of the composition of effective to result in apoptosis of the cells, specifically, where the cancer cells are derived from
10 organs comprising the thymus, colon, liver, breast, ovary, testis, lung, stomach, spleen, kidney, prostate, uterus, skin, head and neck, or the cells are derived from either T-cells or B-cells.

15 This invention also provides for a method of inhibiting the proliferation of virally infected cells, specifically wherein the virally infected cells are infected with the Hepatitis B virus, Epstein-Barr virus, influenza virus, Papilloma virus, Adenovirus, Human T-cell lymphotropic
20 virus, type 1 or HIV.

This invention also provides a pharmaceutical composition comprising compositions capable of inhibiting specific binding between a signal-transducing protein and a
25 cytoplasmic protein.

This invention also provides a pharmaceutical composition comprising compounds identified to be capable of inhibiting specific binding between a signal-transducing
30 protein and a cytoplasmic protein.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1. Diagram of Fas-associated phosphatase-1 protein, showing the six GLGF (PDZ/DHR) domain repeats;
5 comparison of similar membrane binding sites with other proteins and proteins that contain GLGF (PDZ/DHR) repeats.

10 Figures 2A, 2B, 2C and 2D. Mapping of the minimal region of the C-terminal of Fas required for the binding to FAP-1. Numbers at right show each independent clone (Figures 2C and 2D).

2A. Strategy for screening of a random peptide library by the yeast two-hybrid system.

15 2B. Alignment of the C-terminal 15 amino acids of Fas between human (Sequence I.D. No.: 5), rat (Sequence I.D. No.: 6), and mouse (Sequence I.D. No.: 7).

20 2C. The results of screening a semi-random peptide library. Top row indicates the amino acids which were fixed based on the homology between human and rat. Dash lines show unchanged amino acids.

25 2D. The results of screening a random peptide library (Sequence I.D. No.: 8, Sequence I.D. No.: 9, Sequence I.D. No.: 10, Sequence I.D. No.: 11, Sequence I.D. No.: 12, Sequence I.D. No.: 13, Sequence I.D. No.: 14, Sequence I.D. No.: 15, Sequence I.D. No.: 16, Sequence I.D. No.: 17, respectively).

30 Figures 3A, 3B and 3C. Inhibition assay of Fas/FAP-1 binding *in vitro*.

35 3A. Inhibition assay of Fas/FAP-1 binding using the C-terminal 15 amino acids of Fas. GST-Fas fusion protein (191-355) was used for *in vitro* binding assay (lane 1, 3-10). GST-Fas fusion protein (191-320) (lane 2) and 1 mM human PAMP (N-terminal 20 amino acids of proadrenomedullin, M.W. 2460.9)

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(lane 3) were used as negative controls. The concentrations of the C-terminal 15 amino acids added were 1 (lane 4), 3 (lane 5), 10 (lane 6), 30 (lane 7), 100 (lane 8), 300 (lane 9), and 1000 μ M (lane 10).

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3B. Inhibition assay of Fas/FAP-1 binding using the truncated peptides corresponding to the C-terminal 15 amino acids of Fas. All synthetic peptides were acetylated for this inhibition assay (Sequence I.D. No.: 4, Sequence I.D. No.: 18, Sequence I.D. No.: 19, Sequence I.D. No.: 20, Sequence I.D. No.: 21, Sequence I.D. No.: 22, Sequence I.D. No.: 23, respectively).

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3C. Inhibitory effect of Fas/FAP-1 binding using the scanned tripeptides.

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Figures 4A, 4B, 4C and 4D.

4A. Interaction of the C-terminal 3 amino acids of Fas with FAP-1 in yeast.

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4B. Interaction of the C-terminal 3 amino acids of Fas with FAP-1 in vitro.

4C. Immuno-precipitation of native Fas with GST-FAP-1.

4D. Inhibition of Fas/FAP-1 binding with Ac-SLV or Ac-SLY.

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Figures 5A, 5B, 5C, 5D, 5E and 5F. Microinjection of Ac-SLV into the DLD-1 cell line. Triangles identify the cells both that were could be microinjected with Ac-SLV and that showed condensed chromatin identified. On the other hand, only one cell of the area appeared apoptotic when microinjected with Ac-SLY.

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5A. Representative examples of the cells microinjected with Ac-SLV in the presence of 500 ng/ml CH11 are shown in phase contrast.

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5B. Representative examples of the cells microinjected with AC-SLY in the presence of 500 ng/ml CH11 are shown in phase contrast.

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- 5C. Representative examples of the cells microinjected with Ac-SLV in the presence of 500 ng/ml CH11 are shown stained with FITC.
- 5D. Representative examples of the cells microinjected with AC-SLY in the presence of 500 ng/ml CH11 are shown stained with FITC.
- 5E. Representative examples of the cells microinjected with Ac-SLV in the presence of 500 ng/ml CH11 are shown with fluorescent DNA staining with Hoechst 33342.
- 5F. Representative examples of the cells microinjected with AC-SLY in the presence of 500 ng/ml CH11 are shown in fluorescent DNA staining with Hoechst 33342.

Figure 6. Quantitation of apoptosis in microinjected DLD-1 cells.

Figures 7A, 7B, 7C, 7D, 7E, 7F, 7G, and 7H.

- 7A. Amino acid sequence of human nerve growth factor receptor (Sequence I.D. No.: 24).
- 7B. Amino acid sequence of human CD4 receptor (Sequence I.D. No. 25).
- 7C. The interaction of Fas-associated phosphatase-1 to the C-terminal of nerve growth factor receptor (NGFR) (p75).
- 7D. Amino acid sequence of human colorectal mutant cancer protein (Sequence I.D. No.: 26).
- 7E. Amino acid sequence of protein kinase C, alpha type.
- 7F. Amino acid sequence of serotonin 2A receptor (Sequence I.D. No.: 27).
- 7G. Amino acid sequence of serotonin 2B receptor (Sequence I.D. No.: 28).
- 7H. Amino acid sequence of adenomatosis polyposis coli protein (Sequence I.D. No.: 29).

Figure 8. Representation of the structural characteristics of p75 NGFR (low-affinity nerve growth factor receptor).

5 Figure 9. Comparison of the C-terminal ends of Fas and p75 NGFR.

10 Figure 10. In vitro interaction of ³⁵S-labeled FAP-1 with various receptors expressed as GST fusion proteins. The indicated GST fusion proteins immobilized on glutathione-Sepharose beads were incubated with in vitro translated, ³⁵S-labeled FAP-1 protein. After the beads were washed, retained FAP-1 protein was analyzed by SDS-PAGE and autoradiography.

15 Figures 11A and 11B. In vitro interaction ³⁵S-labeled FAP-1 with GST-p75 deletion mutants.

20 11A. Schematic representation of the GST fusion proteins containing the cytoplasmic domains of p75 and p75 deletion mutants. Binding of FAP-1 to the GST fusion proteins with various p75 deletion mutants is depicted at the right and is based on data from (11B).

25 11B. Interaction of in vitro translated, ³⁵S-labeled FAP-1 protein with various GST fusion proteins immobilized on glutathione-Sepharose beads. After the beads were washed, retained FAP-1 protein was analyzed by SDS-PAGE and autoradiography.

30 Figure 12. The association between LexA-C-terminal cytoplasmic region of p75NGFR and VP16-FAP-1. The indicated yeast strains were constructed by transformation and the growth of colonies was tested.
35 +/- indicates the growth of colonies on his⁻ plate.

DETAILED DESCRIPTION OF THE INVENTION

5 As used herein, amino acid residues are abbreviated as follows: A, Ala; C, Cys; D, Asp; E, Glu; F, Phe; G, Gly; H, His; I, Ile; K, Lys; L, Leu; M, Met; N, Asn; P, Pro; Q, Gln; R, Arg; S, Ser; T, Thr; V, Val; W, Trp; and Y, Tyr.

10 In order to facilitate an understanding of the material which follows, certain frequently occurring methods and/or terms are best described in Sambrook, et al., 1989.

15 The present invention provides for a composition capable of inhibiting specific binding between a signal-transducing protein and a cytoplasmic protein containing the amino acid sequence (G/S/A/E)-L-G-(F/I/L), wherein each - represents a peptide bond, each parenthesis
20 encloses amino acids which are alternatives to one other, and each slash within such parentheses separating the alternative amino acids. Further, the cytoplasmic protein may contain the amino acid sequence (K/R/Q)-X_n-(G/S/A/E)-L-G-(F/I/L), wherein X represents any amino acid
25 which is selected from the group comprising the twenty naturally occurring amino acids and n represents at least 2, but not more than 4. Specifically, in a preferred embodiment, the cytoplasmic protein contains the amino acid sequence SLGI.

30 The amino acid sequence (K/R/Q)-X_n-(G/S/A/E)-L-G-(F/I/L) is also well-known in the art as "GLGF (PDZ/DHR) amino acid domain." As used herein, "GLGF (PDZ/DHR) amino acid domain" means the amino acid sequence (K/R/Q)-X_n-(G/S/A/E)-L-G-(F/I/L).
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In a preferred embodiment, the signal-transducing protein

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has at its carboxyl terminus the amino acid sequence (S/T)-X-(V/I/L), wherein each - represents a peptide bond, each parenthesis encloses amino acids which are alternatives to one other, each slash within such parentheses separating the alternative amino acids, and the X represents any amino acid which is selected from the group comprising the twenty naturally occurring amino acids.

The compositions of the subject invention may be, but not limited to, antibodies, inorganic compounds, organic compounds, peptides, peptidomimetic compounds, polypeptides or proteins, fragments or derivatives which share some or all properties, e.g. fusion proteins. The composition may be naturally occurring and obtained by purification, or may be non-naturally occurring and obtained by synthesis.

Specifically, the composition may be a peptide containing the sequence (S/T)-X-(V/I/L)-COOH, wherein each - represents a peptide bond, each parenthesis encloses amino acids which are alternatives to one other, each slash within such parentheses separating the alternative amino acids, the X represents any amino acid which is selected from the group comprising the twenty naturally occurring amino acids. In preferred embodiments, the peptide contains one of the following sequences: DSENSNFRNEIQSLV, RNEIQSLV, NEIQSLV, EIQSLV, IQSLV, QSLV, SLV, IPPDSEDGNEEQSLV, DSEMYNFRSQLASVV, IDLASEFLFLSNSFL, PPTCSQANSGRISTL, SDSNMNMNELSEV, QNFRTYIVSFV, RETIESTV, RGFISLV, TIQSVI, ESLV. A further preferred embodiment would be an organic compound which has the sequence Ac-SLV-COOH, wherein the Ac represents an acetyl and each - represents a peptide bond.

An example of the subject invention is provided infra. Acetylated peptides may be automatically synthesized on

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an Advanced ChemTech ACT357 using previously published procedures by analogy. Wang resin was used for each run and N^α-Fmoc protection was used for all amino acids, and then 20% piperidine/DMF and coupling was completed using
5 DIC/HOBt and subsequently HBTU/DIEA. After the last amino acid was coupled, the growing peptide on the resin was acetylated with Ac₂O/DMF. The acetylated peptide was purified by HPLC and characterized by FAB-MS and ¹H-NMR.

10 Further, one skilled in the art would know how to construct derivatives of the above-described synthetic peptides coupled to non-acetyl groups, such as amines.

15 This invention also provides for a composition capable of inhibiting specific binding between a signal-transducing protein having at its carboxyl terminus the amino acid sequence (S/T)-X-(V/I/L), wherein each - represents a peptide bond, each parenthesis encloses amino acids which are alternatives to one other, each slash within such
20 parentheses separating the alternative amino acids, the X represents any amino acid which is selected from the group comprising the twenty naturally occurring amino acids, and a cytoplasmic protein.

25 The compositions of the subject invention includes antibodies, inorganic compounds, organic compounds, peptides, peptidomimetic compounds, polypeptides or proteins, fragments or derivatives which share some or all properties, e.g. fusion proteins.

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This invention also provides a method of identifying a compound capable of inhibiting specific binding between a signal-transducing protein and a cytoplasmic protein containing the amino acid sequence (G/S/A/E)-L-G-(F/I/L),
35 wherein each - represents a peptide bond, each parenthesis encloses amino acids which are alternatives to one other, each slash within such parentheses

separating the alternative amino acids, which comprises
(a) contacting the cytoplasmic protein bound to the
signal-transducing protein with a plurality of compounds
under conditions permitting binding between a known
5 compound previously shown to be able to displace the
signal-transducing protein bound to the cytoplasmic
protein and the bound cytoplasmic protein to form a
complex; and (b) detecting the displaced signal-
transducing protein or the complex formed in step (a)
10 wherein the displacement indicates that the compound is
capable of inhibiting specific binding between the
signal-transducing protein and the cytoplasmic protein.

The inhibition of the specific binding between the
15 signal-transducing protein and the cytoplasmic protein
may affect the transcription activity of a reporter gene.

Further, in step (b), the displaced cytoplasmic protein
or the complex is detected by comparing the transcription
20 activity of a reporter gene before and after the
contacting with the compound in step (a), where a change
of the activity indicates that the specific binding
between the signal-transducing protein and the
cytoplasmic protein is inhibited and the signal-
transducing protein is displaced.
25

As used herein, the "transcription activity of a reporter
gene" means that the expression level of the reporter
gene will be altered from the level observed when the
30 signal-transducing protein and the cytoplasmic protein
are bound. One can also identify the compound by
detecting other biological functions dependent on the
binding between the signal-transducing protein and the
cytoplasmic protein. Examples of reporter genes are
35 numerous and well-known in the art, including, but not
limited to, histidine resistant genes, ampicillin
resistant genes, β -galactosidase gene.

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Further the cytoplasmic protein may be bound to a solid support. Also the compound may be bound to a solid support and comprises an antibody, an inorganic compound, an organic compound, a peptide, a peptidomimetic compound, a polypeptide or a protein.

An example of the method is provided infra. One can identify a compound capable of inhibiting specific binding between the signal-transducing protein and the cytoplasmic protein using direct methods of detection such as immuno-precipitation of the cytoplasmic protein and the compound bound to a detectable marker. Further, one could use indirect methods of detection that would detect the increase or decrease in levels of gene expression. As discussed infra, one could construct synthetic peptides fused to a LexA DNA binding domain. These constructs would be transformed into the L40-strain with an appropriate cell line having an appropriate reporter gene. One could then detect whether inhibition had occurred by detecting the levels of expression of the reporter gene. In order to detect the expression levels of the reporter gene, one skilled in the art could employ a variety of well-known methods, e.g. two-hybrid systems in yeast, mammals or other cells.

Further, the contacting of step (a) may be in vitro, in vivo, and specifically in an appropriate cell, e.g. yeast cell or mammalian cell. Examples of mammalian cells include, but not limited to, the mouse fibroblast cell NIH 3T3, CHO cells, HeLa cells, Ltk⁻ cells, Cos cells, etc.

Other suitable cells include, but are not limited to, prokaryotic or eukaryotic cells, e.g. bacterial cells (including gram positive cells), fungal cells, insect cells, and other animals cells.

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Further, the signal-transducing protein may be a cell surface receptor, signal transducer protein, or a tumor suppressor protein. Specifically, the cell surface protein is the Fas receptor and may be expressed in cells derived from organs including, but not limited to, thymus, liver, kidney, colon, ovary, breast, testis, spleen, lung, stomach, prostate, uterus, skin, head, and neck, or expressed in cells comprising T-cells and B-cells. In a preferred embodiment, the T-cells are Jurkat T-cells.

Further, the cell-surface receptor may be a CD4 receptor, p75 receptor, serotonin 2A receptor, or serotonin 2B receptor.

Further, the signal transducer protein may be Protein Kinase-C- α -type.

Further, the tumor suppressor protein may be a adenomatosis polyposis coli tumor suppressor protein or colorectal mutant cancer protein.

Further, the cytoplasmic protein contains the amino acid sequence SLGI, specifically Fas-associated phosphatase-1.

This invention also provides a method of identifying a compound capable of inhibiting specific binding between a signal-transducing protein having at its carboxyl terminus the amino acid sequence (S/T)-X-(V/I/L), wherein each - represents a peptide bond, each parenthesis encloses amino acids which are alternatives to one other, each slash within such parentheses separating the alternative amino acids, the X represents any amino acid which is selected from the group comprising the twenty naturally occurring amino acids, and a cytoplasmic protein which comprises (a) contacting the signal-transducing protein bound to the cytoplasmic protein with

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a plurality of compounds under conditions permitting binding between a known compound previously shown to be able to displace the cytoplasmic protein bound to the signal-transducing protein and bound signal-transducing protein to form a complex; and (b) detecting the displaced cytoplasmic protein or the complex of step (a), wherein the displacement indicates that the compound is capable of inhibiting specific binding between the signal-transducing protein and the cytoplasmic protein. The inhibition of the specific binding between the signal-transducing protein and the cytoplasmic protein affects the transcription activity of a reporter gene. Further, in step (b), the displaced signal-transducing protein or the complex is detected by comparing the transcription activity of a reporter gene before and after the contacting with the compound in step (a), where a change of the activity indicates that the specific binding between the signal-transducing protein and the cytoplasmic protein is inhibited and the cytoplasmic protein is displaced.

Further, in step (b), the displaced cytoplasmic protein or the complex is detected by comparing the transcription activity of a reporter gene before and after the contacting with the compound in step (a), where a change of the activity indicates that the specific binding between the signal-transducing protein and the cytoplasmic protein is inhibited and the signal-transducing protein is displaced.

As used herein, the "transcription activity of a reporter gene" means that the expression level of the reporter gene will be altered from the level observed when the signal-transducing protein and the cytoplasmic protein are bound. One can also identify the compound by detecting other biological functions dependent on the binding between the signal-transducing protein and the

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cytoplasmic protein. Examples of reporter genes are numerous and well-known in the art, including, but not limited to, histidine resistant genes, ampicillin resistant genes, β -galactosidase gene.

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Further, the cytoplasmic protein may be bound to a solid support or the compound may be bound to a solid support, comprises an antibody, an inorganic compound, an organic compound, a peptide, a peptidomimetic compound, a polypeptide or a protein.

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An example of the method is provided infra. One could identify a compound capable of inhibiting specific binding between the signal-transducing protein and the cytoplasmic protein using direct methods of detection such as immuno-precipitation of the cytoplasmic protein and the compound bound with a detectable marker. Further, one could use indirect methods of detection that would detect the increase or decrease in levels of gene expression. As discussed infra, one could construct synthetic peptides fused to a LexA DNA binding domain. These constructs would be transformed into L40-strain with an appropriate cell line having a reporter gene. One could then detect whether inhibition had occurred by detecting the levels of the reporter gene. Different methods are also well known in the art, such as employing a yeast two-hybrid system to detect the expression of a reporter gene.

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Further the contacting of step (a) can be in vitro or in vivo, specifically in a yeast cell or a mammalian cell. Examples of mammalian cells include, but not limited to, the mouse fibroblast cell NIH 3T3, CHO cells, HeLa cells, Ltk⁻ cells, Cos cells, etc.

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Other suitable cells include, but are not limited to, prokaryotic or eukaryotic cells, e.g. bacterial cells

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(including gram positive cells), fungal cells, insect cells, and other animals cells.

5 Further, the signal-transducing protein is a cell surface receptor, signal transducer protein, or a tumor suppressor protein. Specifically, the cell surface protein is the Fas receptor and is expressed in cells derived from organs comprising thymus, liver, kidney, colon, ovary, breast, testis, spleen, stomach, prostate, 10 uterus, skin, head and neck, or expressed in cells comprising T-cells and B-cells. In a preferred embodiment, the T-cells are Jurkat T-cells.

15 Further, the cell-surface receptor may be a CD4 receptor, p75 receptor, serotonin 2A receptor, or serotonin 2B receptor.

20 Further, the signal transducer protein may be Protein Kinase-C- α -type.

Further, the tumor suppressor protein may be a adenomatosis polyposis coli tumor suppressor protein or colorectal mutant cancer protein.

25 Further, the cytoplasmic protein contains the amino acid sequence SLGI, specifically Fas-associated phosphatase-1.

30 This invention also provides a method of inhibiting the proliferation of cancer cells comprising the above-described composition, specifically, wherein the cancer cells are derived from organs including, but not limited to, thymus, liver, kidney, colon, ovary, breast, testis, spleen, stomach, prostate, uterus, skin, head and neck, 35 or wherein the cancer cells are derived from cells comprising T-cells and B-cells.

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This invention also provides a method of inhibiting the proliferation of cancer cells comprising the compound identified by the above-described method, wherein the cancer cells are derived from organs including, but not limited to, thymus, liver, kidney, colon, ovary, breast, testis, spleen, stomach, prostate, uterus, skin, head and neck, or wherein the cancer cells are derived from cells comprising T-cells and B-cells.

The invention also provides a method of treating cancer in a subject which comprises introducing to the subject's cancerous cells an amount of the above-described composition effective to result in apoptosis of the cells, wherein the cancer cells are derived from organs including, but not limited to, thymus, liver, kidney, colon, ovary, breast, testis, spleen, stomach, prostate, uterus, skin, head and neck, or wherein the cancer cells are derived from cells comprising T-cells and B-cells.

As used herein "apoptosis" means programmed cell death of the cell. The mechanisms and effects of programmed cell death differs from cell lysis. Some observable effects of apoptosis are: DNA fragmentation and disintegration into small membrane-bound fragments called apoptotic bodies.

Means of detecting whether the composition has been effective to result in apoptosis of the cells are well-known in the art. One means is by assessing the morphological change of chromatin using either phase contrast or fluorescence microscopy.

The invention also provides for a method of inhibiting the proliferation of virally infected cells comprising the above-described composition or the compound identified by the above-described, wherein the virally infected cells comprise Hepatitis B virus, Epstein-Barr

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virus, influenza virus, Papilloma virus, Adeno virus, Human T-cell lymphotropic virus, type 1 or HIV.

5 The invention also provides a method of treating a virally-infected subject which comprises introducing to the subject's virally- infected cells the above-described composition effective to result in apoptosis of the cells or the compound identified by the above-described method of claim 27 effective to result in apoptosis of the
10 cells, wherein the virally infected cells comprise the Hepatitis B virus, Epstein-Barr virus, influenza virus, Papilloma virus, Adeno virus, Human T-cell lymphotropic virus, type 1 or HIV.

15 Means of detecting whether the composition has been effective to result in apoptosis of the cells are well-known in the art. One means is by assessing the morphological change of chromatin using either phase contrast or fluorescence microscopy.

20 This invention also provides for a pharmaceutical composition comprising the above-described composition of in an effective amount and a pharmaceutically acceptable carrier.

25 This invention also provides for a pharmaceutical composition comprising the compound identified by the above-described method of in an effective amount and a pharmaceutically acceptable carrier.

30 This invention further provides a composition capable of specifically binding a signal-transducing protein having at its carboxyl terminus the amino acid sequence (S/T)-X-(V/L/I), wherein each - represents a peptide bond, each
35 parenthesis encloses amino acids which are alternatives to one other, each slash within such parentheses separating the alternative amino acids, and the X

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represents any amino acid which is selected from the group comprising the twenty naturally occurring amino acids. The composition may contain the amino acid sequence (G/S/A/E)-L-G-(F/I/L), wherein each - represents a peptide bond, each parenthesis encloses amino acids which are alternatives to one other, and each slash within such parentheses separating the alternative amino acids. In a preferred embodiment, the composition contains the amino acid sequence (K/R/Q)-X_n-(G/S/A/E)-L-G-(F/I/L). wherein X represents any amino acid which is selected from the group comprising the twenty naturally occurring amino acids and n represents at least 2, but not more than 4. In another preferred embodiment, the composition contains the amino acid sequence SLGI.

This invention further provides a method for identifying compounds capable of binding to a signal-transducing protein having at its carboxyl terminus the amino acid sequence (S/T)-X-(V/L/I), wherein each - represents a peptide bond, each parenthesis encloses amino acids which are alternatives to one other, each slash within such parentheses separating the alternative amino acids, the X represents any amino acid which is selected from the group comprising the twenty naturally occurring amino acids, which comprises (a) contacting the signal-transducing protein with a plurality of compounds under conditions permitting binding between a known compound previously shown to be able to bind to the signal-transducing protein to form a complex; and (b) detecting the complex formed in step (a) so as to identify a compound capable of binding to the signal-transducing protein. Specifically, the identified compound contains the amino acid sequence (G/S/A/E)-L-G-(F/I/L). In a further preferred embodiment, the identified compound contains the amino acid sequence SLGI.

Further, in the above-described method, the signal-

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transducing protein may be bound to a solid support. Also, the compound may be bound to a solid support, and may comprise an antibody, an inorganic compound, an organic compound, a peptide, a peptidomimetic compound,
5 a polypeptide or a protein.

Further, the signal-transducing protein may be a cell-
~~surface receptor or a signal transducer.~~ Specifically,
10 the signal-transducing protein may be the Fas receptor, CD4 receptor, p75 receptor, serotonin 2A receptor, serotonin 2B receptor, or protein kinase-C- α -type.

This invention also provides a method of restoring negative regulation of apoptosis in a cell comprising the
15 above-described composition or a compound identified by the above-described method.

As used herein "restoring negative regulation of apoptosis" means enabling the cell from proceeding onto
20 programmed cell death.

For example, cells that have functional Fas receptors and Fas-associated phosphatase 1 do not proceed onto programmed cell death or apoptosis due to the negative
25 regulation of Fas by the phosphatase. However, if Fas-associated phosphatase 1 is unable to bind to the carboxyl terminus of the Fas receptor ((S/T)-X-(V/L/I) region) , e.g. mutation or deletion of at least one of the amino acids in the amino acid sequence (G/S/A/E)-L-G-
30 (F/I/L), the cell will proceed to apoptosis. By introducing a compound capable of binding to the carboxyl terminus of the Fas receptor, one could mimic the effects of a functional phosphatase and thus restore the negative regulation of apoptosis.

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This invention also provides a method of preventing apoptosis in a cell comprising the above-described

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composition or a compound identified by the above-described method.

5 This invention also provides a means of treating pathogenic conditions caused by apoptosis of relevant cells comprising the above-described composition or the compound identified by the above-described method.

10 This invention is illustrated in the Experimental Details section which follows. These sections are set forth to aid in an understanding of the invention but are not intended to, and should not be construed to, limit in any way the invention as set forth in the claims which follow thereafter.

FIRST SERIES OF EXPERIMENTS

Experimental Details5 **Methods and Materials**

1. Screening a semi-random and random peptide library.

To create numerous mutations in a restricted DNA
10 sequence, PCR mutagenesis with degenerate
oligonucleotides was employed according to a protocol
described elsewhere (Hill, et al. 1987). Based on the
homology between human and rat, two palindromic sequences
were designed for construction of semi-random library.
15 The two primers used were
5'-CGGAATTCNNNNNNNNNAACAGCNNNNNNNNNAATGAANNNCAAAGTCTGNN
NTGAGGATCCTCA-3' (Seq. I.D. No.: 30) and
5'-CGGAATTCGACTCAGAANNNNNNNAACTTCAGANNNNNNNATCNNNNNNNNNGT
CTGAGGATCCTCA-3' (Seq. I.D. No.: 31). Briefly, the two
20 primers (each 200 pmol), purified by HPLC, were annealed
at 70 °C for 5 minutes and cooled at 23 °C for 60 minutes.
A Klenow fragment (5 U) was used for filling in with a
dNTP mix (final concentration, 1 mM per each dNTP) at
23°C for 60 minutes. The reaction was stopped with 1 µl
25 of 0.5 M EDTA and the DNA was purified with ethanol
precipitation. The resulting double-stranded DNA was
digested with EcoRI and BamHI and re-purified by
electrophoresis on non-denaturing polyacrylamide gels.
The double-strand oligonucleotides were then ligated into
30 the EcoRI-BamHI sites of the pBTM116 plasmid. The
ligation mixtures were electroporated into the *E. coli*
XL1-Blue MRF' (Stratagene) for the plasmid library. The
large scale transformation was carried out as previously
reported. The plasmid library was transformed into
35 L40-strain cells (MATa, trp1, leu2, his3, ade2,
LYS2:(lexAop)⁴-HIS3, URA3:: (lexAop)⁸-lacZ) carrying the
plasmid pVP16-31 containing a FAP-1 cDNA (Sato, et al.

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1995). Clones that formed on histidine-deficient medium (His⁺) were transferred to plates containing 40 µg/ml X-gal to test for a blue reaction product (β-gal⁺) in plate and filter assays. The clones selected by His⁺ and β-gal⁺ assay were tested for further analysis. The palindromic oligonucleotide, 5'-CGGAATTC-(NNN)₄₋₁₅-TGAGGATCCTCA-3' (Seq. I.D. No. 32), was used for the construction of the random peptide library.

2. Synthesis of peptides

Peptides were automatically synthesized on an Advanced ChemTech ACT357 by analogy to published procedures (Schnorrenberg and Gerhardt, 1989). Wang resin (0.2-0.3 mmole scale) was used for each run and N^α-Fmoc protection was employed for all amino acids. Deprotection was achieved by treatment with 20% piperidine/DMF and coupling was completed using DIC/HOBt and subsequent HBTU/DIEA. After the last amino acid was coupled, the growing peptide on the resin was acetylated with Ac₂O/DMF. The peptide was cleaved from the resin with concomitant removal of all protecting groups by treating with TFA. The acetylated peptide was purified by HPLC and characterized by FAB-MS and ¹H-NMR.

3. Inhibition assay of Fas/FAP-1 binding using the C-terminal 15 amino acids of Fas.

HFAP-10 cDNA (Sato, et al. 1995) subcloned into the Bluescript vector pSK-II (Stratagene) was in vitro-translated from an internal methionine codon in the presence of ³⁵S-L-methionine using a coupled in vitro transcription/translation system (Promega, TNT lysate) and T7 RNA polymerase. The resulting ³⁵S-labeled protein was incubated with GST-Fas fusion proteins that had been immobilized on GST-Sepharose 4B affinity beads

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(Pharmacia) in a buffer containing 150 mM NaCl, 50 mM Tris [pH 8.0], 5 mM DTT, 2 mM EDTA, 0.1 % NP-40, 1 mM PMSF, 50 µg/ml leupeptin, 1 mM Benzamidine, and 7 µg/ml pepstatin for 16 hours at 4 °C. After washing vigorously
5 4 times in the same buffer, associated proteins were recovered with the glutathione-Sepharose beads by centrifugation, eluted into boiling Laemmli buffer, and analyzed by SDS-PAGE and fluorography.

- 10 4. Inhibition assay of terminal 15 amino acids of Fas and inhibitory effect of Fas/FAP-1 binding using diverse tripeptides.

In vitro-translated [³⁵S]HFAP-1 was purified with a NAP-5
15 column (Pharmacia) and incubated with 3 µM of GST-fusion proteins for 16 hours at 4°C. After washing 4 times in the binding buffer, radioactivity incorporation was determined in a b counter. The percentage of binding inhibition was calculated as follows: percent inhibition
20 = [radioactivity incorporation using GST-Fas (191-335) with peptides - radioactivity incorporation using GST-Fas (191-320) with peptides] / [radioactivity incorporation using GST-Fas (191-335) without peptides - radioactivity incorporation using GST-Fas (191-320) without peptides].
25 n=3.

5. Interaction of the C-terminal 3 amino acids of Fas with FAP-1 in yeast and in vitro.

30 The bait plasmids, pBTM116 (LexA)-SLV, -PLV, -SLY, and -SLA, were constructed and transformed into L40-strain with pVP16-FAP-1 or -ras. Six independent clones from each transformants were picked up for the analysis of growth on histidine-deficient medium. GST-Fas, -SLV, and
35 PLV were purified with GST-Sepharose 4B affinity beads (Pharmacia). The methods for in vitro binding are described above.

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6. Immuno-precipitation of native Fas with GST-FAP-1 and inhibition of Fas/FAP-1 binding with Ac-SLV.

5 GST-fusion proteins with or without FAP-1 were incubated with cell extracts from Jurkat T-cells expressing Fas. The bound Fas was detected by Western analysis using anti-Fas monoclonal antibody (F22120, Transduction Laboratories). The tripeptides, Ac-SLV and Ac-SLY were used for the inhibition assay of Fas/FAP-1 binding.

10 7. Microinjection of Ac-SLV into the DLD-1 cell line. DLD-1 human colon cancer cells were cultured in RPMI 1640 medium containing 10% FCS. For microinjection, cells were plated on CELLocate (Eppendorf) at 1×10^5 cells/2 ml in a 35 mm plastic culture dish and grown for 1 day. Just before microinjection, Fas monoclonal antibodies CH11 (MBL International) was added at the concentration of 500 ng/ml. All microinjection experiments were performed using an automatic microinjection system (Eppendorf transjector 5246, micro-manipulator 5171 and Femtotips) (Pantel, et al. 1995). Synthetic tripeptides were suspended in 0.1% (w/v) FITC-Dextran (Sigma)/K-PBS at the concentration of 100 mM. The samples were microinjected into the cytoplasmic region of DLD-1 cells. Sixteen to 20 hours postinjection, the cells were washed with PBS and stained with 10 μ g/ml Hoechst 33342 in PBS. After incubation at 37°C for 30 minutes, the cells were photographed and the cells showing condensed chromatin were counted as apoptotic.

- 30 8. Quantitation of apoptosis in microinjected DLD-1 cells.

35 For each experiment, 25-100 cells were microinjected. Apoptosis of microinjected cells was determined by assessing morphological changes of chromatin using phase contrast and fluorescence microscopy (Wang, et al., 1995:

McGahon, et al., 1995). The data are means +/- S.D. for two or three independent determinations.

Discussion

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In order to identify the minimal peptide stretch in the C-terminal region of the Fas receptor necessary for FAP-1 binding, an *in vitro* inhibition assay of Fas/FAP-1 binding was used using a series of synthetic peptides as well as yeast two-hybrid system peptide libraries (Figure 2A). First, semi-random libraries (based on the homology between human and rat Fas) (Figures 2B and 2C) of 15 amino acids fused to a LexA DNA binding domain were constructed and co-transformed into yeast strain L40 with pVP16-31 (Sato, et al. 1995) that was originally isolated as FAP-1. After the selection of 200 His⁺ colonies from an initial screen of 5.0×10^6 (Johnson, et al. 1986) transformants, 100 colonies that were β -galactosidase positive were picked for further analysis. Sequence analysis of the library plasmids encoding the C-terminal 15 amino acids revealed that all of the C-termini were either valine, leucine or isoleucine residues. Second, a random library of 4-15 amino acids fused to a LexA DNA binding domain was constructed and screened according to this strategy (Figure 2D). Surprisingly, all of the third amino acid residues from the C-termini were serine, and the results of C-terminal amino acid analyses were identical to the screening of the semi-random cDNA libraries. No other significant amino acid sequences were found in these library screenings, suggesting that the motifs of the last three amino acids (tS-X-V/L/I) are very important for the association with the third PDZ domain of FAP-1 and play a crucial role in protein-protein interaction as well as for the regulation of Fas-induced apoptosis. To further confirm whether the last three amino acids are necessary and sufficient for Fas/FAP-1 binding, plasmids of the LexA-SLV, -PLV, -PLY,

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-SLY, and -SLA fusion proteins were constructed and co-transformed into yeast with pVP16-FAP-1. The results showed that only LexA-SLV associated with FAP-1, whereas LexA-PLV, -PLY, -SLY, and -SLA did not (Figure 4A). In vitro binding studies using various GST-tripeptide fusions and in vitro-translated FAP-1 were consistent with these results (Figure 4B).

In addition to yeast two-hybrid approaches, in vitro inhibition assay of Fas/FAP-1 binding was also used. First, a synthetic peptide of the C-terminal 15 amino acids was tested whether it could inhibit the binding of Fas and FAP-1 in vitro (Figure 3A). The binding of in vitro-translated FAP-1 to GST-Fas was dramatically reduced and dependent on the concentration of the synthetic 15 amino acids of Fas. In contrast with these results, human PAMP peptide (Kitamura, et al. 1994) as a negative control had no effect on Fas/FAP-1 binding activity under the same biochemical conditions. Second, the effect of truncated C-terminal synthetic peptides of Fas on Fas/FAP-1 binding in vitro was examined. As shown in Figure 3B, only the three C-terminal amino acids (Ac-SLV) were sufficient to obtain the same level of inhibitory effect on the binding of FAP-1 to Fas as achieved with the 4-15 synthetic peptides. Furthermore, Fas/FAP-1 binding was extensively investigated using the scanned tripeptides to determine the critical amino acids residues required for inhibition (Figure 3C). The results revealed that the third amino acids residues from the C-terminus, and the C-terminal amino acids having the strongest inhibitory effect were either serine or threonine; and either valine, leucine, or isoleucine, respectively. However, there were no differences among the second amino acid residues from the C-terminus with respect to their inhibitory effect on Fas/FAP-1 binding. These results were consistent with those of the yeast two-hybrid system (Figures 2C and 2D). Therefore, it was

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concluded that the C-terminal three amino acids (SLV) are critical determinants of Fas binding to the third PDZ domain of FAP-1 protein.

5 To further substantiate that the PDZ domain interacts with tS/T-X-V/L/I under more native conditions, GST-fused FAP-1 proteins were tested for their ability to interact with Fas expressed in Jurkat T-cells. The results revealed that the tripeptide Ac-SLV, but not Ac-SLY,
10 abolished in a dose-dependent manner the binding activity of FAP-1 to Fas proteins extracted from Jurkat T-cells (Figures 4C and 4D). This suggests that the C-terminal amino acids tSLV are the minimum binding site for FAP-1, and that the amino acids serine and valine are critical
15 for this physical association.

To next examine the hypothesis that the physiological association between the C-terminal three amino acids of Fas and the third PDZ domain of FAP-1 is necessary for
20 the *in vivo* function of FAP-1 as a negative regulator of Fas-mediated signal transduction, a microinjection experiment was employed with synthetic tripeptides in a colon cancer cell line, DLD-1, which expresses both Fas and FAP-1, and is resistant to Fas-induced apoptosis.
25 The experiments involved the direct microinjection of the synthetic tripeptides into the cytoplasmic regions of single cells and the monitoring of the physiological response to Fas-induced apoptosis *in vivo*. The results showed that microinjection of Ac-SLV into DLD-1 cells
30 dramatically induced apoptosis in the presence of Fas-monoclonal antibodies (CH11, 500 ng/ml) (Figures 5A, 5E and Figure 6), but that microinjection of Ac-SLY and PBS/K did not (Figures 5B, 5F and Figure 6). These results strongly support the hypothesis that the physical
35 association of FAP-1 with the C-terminus of Fas is essential for protecting cells from Fas-induced apoptosis.

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In summary, it was found that the C-terminal SLV of Fas is alone necessary and sufficient for binding to the third PDZ domain of FAP-1. Secondly, it is proposed that the new consensus motif of tS/T-X-V/L/I for such binding to the PDZ domain, instead of tS/T-X-V. It is therefore possible that FAP-1 plays important roles for the modulation of signal transduction pathways in addition to its physical interaction with Fas. Thirdly, it is demonstrated that the targeted induction of Fas-mediated apoptosis in colon cancer cells by direct microinjection of the tripeptide Ac-SLV. Further investigations including the identification of a substrate(s) of FAP-1 and structure-function analysis will provide insight to the potential therapeutic applications of Fas/FAP-1 interaction in cancer as well as provide a better understanding of the inhibitory effect of FAP-1 on Fas-mediated signal transduction.

SECOND SERIES OF EXPERIMENTS

FAP-1 was originally identified as a membrane-associated protein tyrosine phosphatase which binds to the C-terminus of Fas, and possesses six PDZ domains (also known as DHR domain or GLGF repeat). PDZ domain has recently been shown as a novel module for specific protein-protein interaction, and it appears to be important in the assembly of membrane proteins and also in linking signaling molecules in a multiprotein complex. In recent comprehensive studies, it was found that the third PDZ domain of FAP-1 specifically recognized the sequence motif t(S/T)-X-V and interacts with the C-terminal three amino acids SLV of Fas (Fig. 9). In order to investigate the possibility that FAP-1 also interacts with the C-terminal region of p75NGFR (Fig. 8), an in vitro binding assay, was performed as well as, a yeast two-hybrid analysis by using a series of deletion mutants of p75NGFR. The results revealed that the C-terminal cytoplasmic region of p75NGFR, which is highly conserved among all species, interacts with FAP-1 (Fig. 10). Furthermore, the C-terminal three amino acids SPV of p75NGFR were necessary and sufficient for the interaction with the third PDZ domain of FAP-1 (Fig. 11A and 11B). Since FAP-1 expression was found highest in fetal brain, these findings imply that interaction of FAP-1 with p75NGFR plays an important role for signal transduction pathway via p75NGFR in neuronal cells as well as in the formation of the initial signal-transducing complex for p75NGFR.

REFERENCES

1. Banville, D., et al. J. Biol.Chem. 269: 22320-22327 (1994).
- 5 2. Boldin, M. P. et al. J. Biol. Chem. 270: 7795-7798 (1995).
3. Camerini, D., et al. J. Immunol. 147: 3165-3169 (1991).
- 10 4. Chao, M.V. and B.L. Hempstead TINS 18: 321-326 (1995).
- 15 5. Chinnaiyan, A. M., et al. Cell 81: 505-512 (1995).
6. Cho, K.-O., et al. Neuron 9: 929-942 (1992).
7. Conboy, J. G., et al. J. Biol. Chem. 266: 8273-8280 (1991).
- 20 8. Doyle, D.A., et al. Cell 85: 1067-1076 (1996).
9. Funayama, N., et al. J. Cell Biol. 115: 1039-1048 (1991).
- 25 10. Gould, K. L., et al. EMBO J. 8: 4133-4142 (1989).
11. Gu, M. X., et al. Proc. Natl. Acad. Sci. U.S.A. 88: 5867-5871 (1991).
- 30 12. Hill, D. E., et al. Meth. Enzymol. 155, 558-568 (1987).
13. Ito, N., and Nagata, S. J. Biol. Chem. 268: 10932-10937 (1993).

14. Itoh, N. et al. Cell 66: 233-243 (1991).
15. Johnson, D. et al. Cell 47: 545-554 (1986).
- 5 16. Kim, E., et al. Nature 378: 85-88 (1995).
17. Kischkel, F. C. et al. EMBO J. 14: 5579-5588 (1995).
-
18. Kitamura, K. et al. FEBS Lett. 351: 35-37 (1994).
- 10 19. Kornau, H.-C., et al. Science 269:1737-1740 (1995).
20. Lankes, W. T., and Furthmayr, H. Proc. Natl. Acad. Sci. U.S.A. 88: 8297-8301 (1991).
- 15 21. Maekawa, K., et al. FEBS Letters 337: 200-206 (1994).
22. Mallett, S., et al. EMBO J. 9: 1063-1068 (1990).
- 20 23. Matsumine, A. et al. Science 272: 1020-1023 (1996).
24. McGahon, A. J. et al. Meth. Cell Biol. 46: 153-185 (1995).
- 25 25. Pantel, K. et al. J. Natl. Cancer Inst. 87: 1162-1168 (1995).
26. Rouleau, G. et al. Nature 363: 515-521 (1993).
- 30 27.
28. Sambrook, J., et al. (1989) Molecular Cloning: a laboratory manual. Second Edition. Cold Spring Harbor Laboratory Press.
- 35 29. Sato, T., et al. Science 268: 411-415 (1995).
30. Schnorrenberg, G. and Gerhardt H. Tetrahedron 45:

7759-7764 (1989).

- 5
31. Saras, J., et al. J. Biol. Chem. 269, 24082-24089 (1994).
32. Smith, C. A. et al. Cell 73: 1349-1360 (1993).
33. Stamenkovic, I., et al. EMBO J. 8: 1403-1410 (1989).
- 10
34. Stanger, B. Z., et al. Cell 81: 513-523 (1995).
35. Takahashi, T. et al. Cell 76: 969-976 (1994).
- 15
36. Vogel, W., et al. (1993). Science 259: 1611-1614 (1993).
37. Watanabe-Fukunaga, R., et al. Nature 356: 314-317 (1992).
- 20
38. Wang, X. W., et al. Cancer Res. 55: 6012-6016 (1995).
39. Westendorp, M. O. et al. Nature 375: 497-500 (1995).
- 25
40. Woods, D.F. and Bryant, P.J. Cell 66: 451-464 (1991).
- 30
41. Yang, Q., and Tonks, N. K. Proc. Natl. Acad. Sci. U.S.A. 88: 5949-5953 (1991).

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SEQUENCE LISTING

(1) GENERAL INFORMATION:

- 5 (i) APPLICANT: Takaaki Sato and Junn Yanagisawa
- 10 (ii) TITLE OF INVENTION: COMPOUNDS THAT INHIBIT THE
INTERACTION BETWEEN SIGNAL-
TRANSDUCING PROTEINS AND THE GLGF
(PDZ/DHR) DOMAIN AND USES THEREOF
- (iii) NUMBER OF SEQUENCES: 33
- 15 (iv) CORRESPONDENCE ADDRESS:
(A) ADDRESSEE: Cooper & Dunham LLP
(B) STREET: 1185 Avenue of the Americas
(C) CITY: New York
(D) STATE: New York
20 (E) COUNTRY: U.S.A.
(F) ZIP: 10036
- (v) COMPUTER READABLE FORM:
25 (A) MEDIUM TYPE: Floppy disk
(B) COMPUTER: IBM PC compatible
(C) OPERATING SYSTEM: PC-DOS/MS-DOS
(D) SOFTWARE: PatentIn Release #1.0, Version #1.30
- (vi) CURRENT APPLICATION DATA:
30 (A) APPLICATION NUMBER: Not Yet Known
(B) FILING DATE: 18-JUL-1997
(C) CLASSIFICATION:
- 35 (viii) ATTORNEY/AGENT INFORMATION:
(A) NAME: White, John P
(B) REGISTRATION NUMBER: 28,678
(C) REFERENCE/DOCKET NUMBER: 0575/48962-A-PCT/JPW/JKM
- 40 (ix) TELECOMMUNICATION INFORMATION:
(A) TELEPHONE: (212) 278-0400
(B) TELEFAX: (212) 391-0525

(2) INFORMATION FOR SEQ ID NO:1:

- 45 (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 4 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
- 50 (ii) MOLECULE TYPE: peptide
- (iii) HYPOTHETICAL: NO
- 55 (iv) ANTI-SENSE: NO
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:
Gly/Ser/Ala/Glu Leu Gly Phe/Ile/Leu
60 1

(2) INFORMATION FOR SEQ ID NO:2:

- 65 (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 6 amino acids
(B) TYPE: amino acid

-37-

(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

Lys/Arg/Gln Xaa(n) Gly/Ser/Ala/Glu Leu Gly Phe/Ile/Leu
1 5

(2) INFORMATION FOR SEQ ID NO:3:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 4 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

Ser Leu Gly Ile
1

(2) INFORMATION FOR SEQ ID NO:4:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 6 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

Ser/Thr Xaa Val/Ile/Leu
1

(2) INFORMATION FOR SEQ ID NO:5:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

-38-

Asp Ser Glu Asn Ser Asn Phe Arg Asn Glu Ile Gln Ser Leu Val
1 5 10 15

5 (2) INFORMATION FOR SEQ ID NO:6:

(i) SEQUENCE CHARACTERISTICS:
10 (A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

15 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

Ser Ile Ser Asn Ser Arg Asn Glu Asn Glu Gly Gln Ser Leu Glu
1 5 10 15

20 (2) INFORMATION FOR SEQ ID NO:7:

(i) SEQUENCE CHARACTERISTICS:
25 (A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

30 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

Ser Thr Pro Asp Thr Gly Asn Glu Asn Glu Gly Gln Cys Leu Glu
1 5 10 15

35

(2) INFORMATION FOR SEQ ID NO:8:

(i) SEQUENCE CHARACTERISTICS:
40 (A) LENGTH: 4 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

45 (ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:

Glu Ser Leu Val
50 1

(2) INFORMATION FOR SEQ ID NO:9:

(i) SEQUENCE CHARACTERISTICS:
55 (A) LENGTH: 6 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

60 (ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:

65 Thr Ile Gln Ser Val Ile
1 5

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(2) INFORMATION FOR SEQ ID NO:10:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 8 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:

Arg Gly Phe Ile Ser Ser Leu Val
1 5

(2) INFORMATION FOR SEQ ID NO:11:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 8 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:

Arg Glu Thr Ile Glu Ser Thr Val
1 5

(2) INFORMATION FOR SEQ ID NO:12:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 11 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:

Gln Asn Phe Arg Thr Tyr Ile Val Ser Phe Val
1 5 10

(2) INFORMATION FOR SEQ ID NO:13:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 13 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:13:

Ser Asp Ser Asn Met Asn Met Asn Glu Leu Ser Glu Val
1 5 10

(2) INFORMATION FOR SEQ ID NO:14:

(i) SEQUENCE CHARACTERISTICS:

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(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

5 (ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:

10 Pro Pro Thr Cys Ser Gln Ala Asn Ser Gly Arg Ile Ser Thr Leu
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:15:

15 (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
20 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:15:

25 Ile Asp Leu Ala Ser Glu Phe Leu Phe Leu Ser Asn Ser Phe Leu
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:16:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
35 (C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:16:

40 Asp Ser Glu Met Tyr Asn Phe Arg Ser Gln Leu Ala Ser Val Val
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:17:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
50 (C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:17:

55 Ile Pro Pro Asp Ser Glu Asp Gly Asn Glu Glu Gln Ser Leu Val
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:18:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 4 amino acids
65 (B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

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(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:18:

5 Gln Ser Leu Val
 1

(2) INFORMATION FOR SEQ ID NO:19:

10 (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 5 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS: single
15 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:19:

20 Ile Gln Ser Leu Val
 1 5

(2) INFORMATION FOR SEQ ID NO:20:

(i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 6 amino acids
 (B) TYPE: amino acid
30 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:20:

35 Glu Ile Gln Ser Leu Val
 1 5

(2) INFORMATION FOR SEQ ID NO:21:

(i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 7 amino acids
 (B) TYPE: amino acid
45 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:21:

50 Asn Glu Ile Gln Ser Leu Val
 1 5

(2) INFORMATION FOR SEQ ID NO:22:

(i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 8 amino acids
60 (B) TYPE: amino acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

65 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:22:

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Arg Asn Glu Ile Gln Ser Leu Val
1 5

5 (2) INFORMATION FOR SEQ ID NO:23:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
10 (C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

15 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:23:

Asp Ser Glu Asn Ser Asn Phe Arg Asn Glu Ile Gln Ser Leu Val
1 5 10 15

20 (2) INFORMATION FOR SEQ ID NO:24:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 427 amino acids
25 (B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

30 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:24:

Met Gly Ala Gly Ala Thr Gly Arg Ala Met Asp Gly Pro Arg Leu Leu
1 5 10 15

35 Leu Leu Leu Leu Leu Gly Val Ser Leu Gly Gly Ala Lys Glu Ala Cys
20 25 30

40 Pro Thr Gly Leu Tyr Thr His Ser Gly Glu Cys Cys Lys Ala Cys Asn
35 40 45

Leu Gly Glu Gly Val Ala Gln Pro Cys Gly Ala Asn Gln Thr Val Cys
50 55 60

45 Glu Pro Cys Leu Asp Ser Val Thr Phe Ser Asp Val Val Ser Ala Thr
65 70 75 80

Glu Pro Cys Lys Pro Cys Thr Glu Cys Val Gly Leu Gln Ser Met Ser
85 90 95

50 Ala Pro Cys Val Glu Ala Asp Asp Ala Val Cys Arg Cys Ala Tyr Gly
100 105 110

55 Tyr Tyr Gln Asp Glu Thr Thr Gly Arg Cys Glu Ala Cys Arg Val Cys
115 120 125

Glu Ala Gly Ser Gly Leu Val Phe Ser Cys Gln Asp Lys Gln Asn Thr
130 135 140

60 Val Cys Glu Glu Cys Pro Asp Gly Thr Tyr Ser Asp Glu Ala Asn His
145 150 155 160

Val Asp Pro Cys Leu Pro Cys Thr Val Cys Glu Asp Thr Glu Arg Gln
165 170 175

65 Leu Arg Glu Cys Thr Arg Trp Ala Asp Ala Glu Cys Glu Glu Ile Pro
180 185 190

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	Gly	Arg	Trp	Ile	Thr	Arg	Ser	Thr	Pro	Pro	Glu	Gly	Ser	Asp	Ser	Thr
			195					200					205			
5	Ala	Pro	Ser	Thr	Gln	Glu	Pro	Glu	Ala	Pro	Pro	Glu	Gln	Asp	Leu	Ile
		210					215					220				
	Ala	Ser	Thr	Val	Ala	Gly	Val	Val	Thr	Thr	Val	Met	Gly	Ser	Ser	Gln
	225					230					235					240
10	Pro	Val	Val	Thr	Arg	Gly	Thr	Thr	Asp	Asn	Leu	Ile	Pro	Val	Tyr	Cys
					245					250					255	
	Ser	Ile	Leu	Ala	Ala	Val	Val	Val	Gly	Leu	Val	Ala	Tyr	Ile	Ala	Phe
15				260					265					270		
	Lys	Arg	Trp	Asn	Ser	Cys	Lys	Gln	Asn	Lys	Gly	Gly	Ala	Asn	Ser	Arg
			275					280					285			
20	Pro	Val	Asn	Gln	Thr	Pro	Pro	Pro	Glu	Gly	Glu	Lys	Ile	His	Ser	Asp
		290				295						300				
	Ser	Gly	Ile	Ser	Val	Asp	Ser	Gln	Ser	Leu	His	Asp	Gln	Gln	Pro	His
	305					310					315					320
25	Thr	Gln	Thr	Ala	Ser	Gly	Gln	Ala	Leu	Lys	Gly	Asp	Gly	Gly	Leu	Tyr
					325					330					335	
	Ser	Ser	Leu	Pro	Pro	Ala	Lys	Arg	Glu	Glu	Val	Glu	Lys	Leu	Leu	Asn
30				340					345					350		
	Gly	Ser	Ala	Gly	Asp	Thr	Trp	Arg	His	Leu	Ala	Gly	Glu	Leu	Gly	Tyr
			355					360					365			
35	Gln	Pro	Glu	His	Ile	Asp	Ser	Phe	Thr	His	Glu	Ala	Cys	Pro	Val	Arg
		370					375					380				
	Ala	Leu	Leu	Ala	Ser	Trp	Ala	Thr	Gln	Asp	Ser	Ala	Thr	Leu	Asp	Ala
	385					390					395					400
40	Leu	Leu	Ala	Ala	Leu	Arg	Arg	Ile	Gln	Arg	Ala	Asp	Leu	Val	Glu	Ser
					405					410					415	
45	Leu	Cys	Ser	Glu	Ser	Thr	Ala	Thr	Ser	Pro	Val					
				420					425							

(2) INFORMATION FOR SEQ ID NO:25:

(i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 458 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:25:

Met	Asn	Arg	Gly	Val	Pro	Phe	Arg	His	Leu	Leu	Leu	Val	Leu	Gln	Leu
1				5					10					15	
Ala	Leu	Leu	Pro	Ala	Ala	Thr	Gln	Gly	Lys	Lys	Val	Val	Leu	Gly	Lys
			20					25					30		
Lys	Gly	Asp	Thr	Val	Glu	Leu	Thr	Cys	Thr	Ala	Ser	Gln	Lys	Lys	Ser
		35					40					45			

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	Ile	Gln	Phe	His	Trp	Lys	Asn	Ser	Asn	Gln	Ile	Lys	Ile	Leu	Gly	Asn	
	50						55					60					
5	Gln	Gly	Ser	Phe	Leu	Thr	Lys	Gly	Pro	Ser	Lys	Leu	Asn	Asp	Arg	Ala	
	65					70					75					80	
	Asp	Ser	Arg	Arg	Ser	Leu	Trp	Asp	Gln	Gly	Asn	Phe	Pro	Leu	Ile	Ile	
					85					90					95		
10	Lys	Asn	Leu	Lys	Ile	Glu	Asp	Ser	Asp	Thr	Tyr	Ile	Cys	Glu	Val	Glu	
				100					105					110			
	Asp	Gln	Lys	Glu	Glu	Val	Gln	Leu	Leu	Val	Phe	Gly	Leu	Thr	Ala	Asn	
			115					120					125				
15	Ser	Asp	Thr	His	Leu	Leu	Gln	Gly	Gln	Ser	Leu	Thr	Ile	Thr	Leu	Glu	
		130					135					140					
	Ser	Pro	Pro	Gly	Ser	Ser	Pro	Ser	Val	Gln	Cys	Arg	Ser	Pro	Arg	Gly	
20		145				150					155					160	
	Lys	Asn	Ile	Gln	Gly	Gly	Lys	Thr	Leu	Ser	Val	Ser	Gln	Leu	Glu	Leu	
				165						170					175		
25	Gln	Asp	Ser	Gly	Thr	Trp	Thr	Cys	Thr	Val	Leu	Gln	Asn	Gln	Lys	Lys	
				180					185					190			
	Val	Glu	Phe	Lys	Ile	Asp	Ile	Val	Val	Leu	Ala	Phe	Gln	Lys	Ala	Ser	
			195					200					205				
30	Ser	Ile	Val	Tyr	Lys	Lys	Glu	Gly	Glu	Gln	Val	Glu	Phe	Ser	Phe	Pro	
		210					215					220					
	Leu	Ala	Phe	Thr	Val	Glu	Lys	Leu	Thr	Gly	Ser	Gly	Glu	Leu	Trp	Trp	
35		225				230					235					240	
	Gln	Ala	Glu	Arg	Ala	Ser	Ser	Ser	Lys	Ser	Trp	Ile	Thr	Phe	Asp	Leu	
				245						250					255		
40	Lys	Asn	Lys	Glu	Val	Ser	Val	Lys	Arg	Val	Thr	Gln	Asp	Pro	Lys	Leu	
				260					265					270			
	Gln	Met	Gly	Lys	Lys	Leu	Pro	Leu	His	Leu	Thr	Leu	Pro	Gln	Ala	Leu	
		275						280					285				
45	Pro	Gln	Tyr	Ala	Gly	Ser	Gly	Asn	Leu	Thr	Leu	Ala	Leu	Glu	Ala	Lys	
		290					295					300					
	Thr	Gly	Lys	Leu	His	Gln	Glu	Asn	Val	Leu	Val	Val	Met	Arg	Ala	Thr	
50		305				310					315					320	
	Gln	Leu	Gln	Lys	Asn	Leu	Thr	Cys	Glu	Val	Trp	Gly	Pro	Thr	Ser	Pro	
				325						330					335		
55	Lys	Leu	Met	Leu	Ser	Leu	Lys	Leu	Glu	Asn	Lys	Glu	Ala	Lys	Val	Ser	
			340						345					350			
	Lys	Arg	Glu	Lys	Ala	Val	Trp	Val	Leu	Asn	Pro	Glu	Ala	Gly	Met	Trp	
			355					360					365				
60	Gln	Cys	Leu	Leu	Ser	Asp	Ser	Gly	Gln	Val	Leu	Leu	Glu	Ser	Asn	Ile	
		370					375					380					
	Lys	Val	Leu	Pro	Thr	Trp	Ser	Thr	Pro	Val	Gln	Pro	Met	Ala	Leu	Ile	
65		385				390					395					400	
	Val	Leu	Gly	Gly	Val	Ala	Gly	Leu	Leu	Leu	Phe	Ile	Gly	Leu	Gly	Ile	

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				405					410					415		
	Phe	Phe	Cys	Val	Arg	Cys	Arg	His	Arg	Arg	Arg	Gln	Ala	Glu	Arg	Met
				420					425					430		
5	Ser	Gln	Ile	Lys	Arg	Leu	Leu	Ser	Glu	Lys	Lys	Glu	Cys	Gln	Cys	Pro
			435					440					445			
10	His	Arg	Phe	Gln	Lys	Thr	Cys	Ser	Pro	Ile						
		450					455									

(2) INFORMATION FOR SEQ ID NO:26:

15 (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 828 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

20 (ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:26:

25	Met	Asn	Ser	Gly	Val	Ala	Met	Lys	Tyr	Gly	Asn	Asp	Ser	Ser	Ala	Glu
	1				5					10					15	
	Leu	Ser	Glu	Leu	His	Ser	Ala	Ala	Leu	Ala	Ser	Leu	Lys	Gly	Asp	Ile
				20					25					30		
30	Val	Glu	Leu	Asn	Lys	Arg	Leu	Gln	Thr	Glu	Arg	Glu	Asp	Leu	Leu	
			35				40					45				
35	Glu	Lys	Lys	Leu	Ala	Lys	Ala	Gln	Cys	Glu	Gln	Ser	His	Leu	Met	Arg
		50				55						60				
	Glu	His	Glu	Asp	Val	Gln	Glu	Arg	Thr	Thr	Leu	Arg	Tyr	Glu	Glu	Arg
	65				70						75				80	
40	Ile	Thr	Glu	Leu	His	Ser	Val	Ile	Ala	Glu	Leu	Asn	Lys	Lys	Ile	Asp
				85						90					95	
	Arg	Leu	Gln	Gly	Thr	Thr	Ile	Arg	Glu	Glu	Asp	Glu	Tyr	Ser	Glu	Leu
			100						105					110		
45	Arg	Ser	Glu	Leu	Ser	Gln	Ser	Gln	His	Glu	Val	Asn	Glu	Asp	Ser	Arg
			115				120						125			
	Ser	Met	Asp	Gln	Asp	Gln	Thr	Ser	Val	Ser	Ile	Pro	Glu	Asn	Gln	Ser
50		130				135						140				
	Thr	Met	Val	Thr	Ala	Asp	Met	Asp	Asn	Cys	Ser	Asp	Ile	Asn	Ser	Glu
	145				150						155				160	
55	Leu	Gln	Arg	Val	Leu	Thr	Gly	Leu	Glu	Asn	Val	Val	Cys	Gly	Arg	Lys
				165						170					175	
	Lys	Ser	Ser	Cys	Ser	Leu	Ser	Val	Ala	Glu	Val	Asp	Arg	His	Ile	Glu
			180						185					190		
60	Gln	Leu	Thr	Thr	Ala	Ser	Glu	His	Cys	Asp	Leu	Ala	Ile	Lys	Thr	Val
			195				200						205			
	Glu	Glu	Ile	Glu	Gly	Val	Leu	Gly	Arg	Asp	Leu	Tyr	Pro	Asn	Leu	Ala
65		210				215					220					
	Glu	Glu	Arg	Ser	Arg	Trp	Glu	Lys	Glu	Leu	Ala	Gly	Leu	Arg	Glu	Glu

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	225				230					235					240	
	Asn	Glu	Ser	Leu	Thr	Ala	Met	Leu	Cys	Ser	Lys	Glu	Glu	Glu	Leu	Asn
					245					250					255	
5	Arg	Thr	Lys	Ala	Thr	Met	Asn	Ala	Ile	Arg	Glu	Glu	Arg	Asp	Arg	Leu
				260					265					270		
	Arg	Arg	Arg	Val	Arg	Glu	Leu	Gln	Thr	Arg	Leu	Gln	Ser	Val	Gln	Ala
10			275					280					285			
	Thr	Gly	Pro	Ser	Ser	Pro	Gly	Arg	Leu	Thr	Ser	Thr	Asn	Arg	Pro	Ile
		290					295					300				
15	Asn	Pro	Ser	Thr	Gly	Glu	Leu	Ser	Thr	Ser	Ser	Ser	Ser	Asn	Asp	Ile
	305					310					315					320
	Pro	Ile	Ala	Lys	Ile	Ala	Glu	Arg	Val	Lys	Leu	Ser	Lys	Thr	Arg	Ser
					325					330					335	
20	Glu	Ser	Ser	Ser	Ser	Asp	Arg	Pro	Val	Leu	Gly	Ser	Glu	Ile	Ser	Ser
				340					345					350		
	Ile	Gly	Val	Ser	Ser	Ser	Val	Ala	Glu	His	Leu	Ala	His	Ser	Leu	Gln
25				355				360					365			
	Asp	Cys	Ser	Asn	Ile	Gln	Glu	Ile	Phe	Gln	Thr	Leu	Tyr	Ser	His	Gly
		370					375					380				
30	Ser	Ala	Ile	Ser	Glu	Ser	Lys	Ile	Arg	Glu	Phe	Glu	Val	Glu	Thr	Glu
	385					390					395					400
	Arg	Leu	Asn	Ser	Arg	Ile	Glu	His	Leu	Lys	Ser	Gln	Asn	Asp	Leu	Leu
					405					410					415	
35	Thr	Ile	Thr	Leu	Glu	Glu	Cys	Lys	Ser	Asn	Ala	Glu	Arg	Met	Ser	Met
				420					425					430		
	Leu	Val	Gly	Lys	Tyr	Glu	Ser	Asn	Ala	Thr	Ala	Leu	Arg	Leu	Ala	Leu
40			435					440					445			
	Gln	Tyr	Ser	Glu	Gln	Cys	Ile	Glu	Ala	Tyr	Glu	Leu	Leu	Leu	Ala	Leu
		450					455					460				
45	Ala	Glu	Ser	Glu	Gln	Ser	Leu	Ile	Leu	Gly	Gln	Phe	Arg	Ala	Ala	Gly
	465					470					475					480
	Val	Gly	Ser	Ser	Pro	Gly	Asp	Gln	Ser	Gly	Asp	Glu	Asn	Ile	Thr	Gln
					485					490					495	
50	Met	Leu	Lys	Arg	Ala	His	Asp	Cys	Arg	Lys	Thr	Ala	Glu	Asn	Ala	Ala
				500					505					510		
	Lys	Ala	Leu	Leu	Met	Lys	Leu	Asp	Gly	Ser	Cys	Gly	Gly	Ala	Phe	Ala
55			515					520					525			
	Val	Ala	Gly	Cys	Ser	Val	Gln	Pro	Trp	Glu	Ser	Leu	Ser	Ser	Asn	Ser
		530					535					540				
60	His	Thr	Ser	Thr	Thr	Ser	Ser	Thr	Ala	Ser	Ser	Cys	Asp	Thr	Glu	Phe
	545					550					555					560
	Thr	Lys	Glu	Asp	Glu	Gln	Arg	Leu	Lys	Asp	Tyr	Ile	Gln	Gln	Leu	Lys
					565					570					575	
65	Asn	Asp	Arg	Ala	Ala	Val	Lys	Leu	Thr	Met	Leu	Glu	Leu	Glu	Ser	Ile
				580					585					590		

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	His	Ile	Asp	Pro	Leu	Ser	Tyr	Asp	Val	Lys	Pro	Arg	Gly	Asp	Ser	Gln
			595					600					605			
5	Arg	Leu	Asp	Leu	Glu	Asn	Ala	Val	Leu	Met	Gln	Glu	Leu	Met	Ala	Met
	610						615					620				
	Lys	Glu	Glu	Met	Ala	Glu	Leu	Lys	Ala	Gln	Leu	Tyr	Leu	Leu	Glu	Lys
	625					630					635					640
10	Glu	Lys	Lys	Ala	Leu	Glu	Leu	Lys	Leu	Ser	Thr	Arg	Glu	Ala	Gln	Glu
					645					650					655	
	Gln	Ala	Tyr	Leu	Val	His	Ile	Glu	His	Leu	Lys	Ser	Glu	Val	Glu	Glu
				660					665					670		
15	Gln	Lys	Glu	Gln	Arg	Met	Arg	Ser	Leu	Ser	Ser	Thr	Ser	Ser	Gly	Ser
			675					680					685			
	Lys	Asp	Lys	Pro	Gly	Lys	Glu	Cys	Ala	Asp	Ala	Ala	Ser	Pro	Ala	Leu
20		690					695					700				
	Ser	Leu	Ala	Glu	Leu	Arg	Thr	Thr	Cys	Ser	Glu	Asn	Glu	Leu	Ala	Ala
	705					710					715					720
25	Glu	Phe	Thr	Asn	Ala	Ile	Arg	Arg	Glu	Lys	Lys	Leu	Lys	Ala	Arg	Val
				725						730					735	
	Gln	Glu	Leu	Val	Ser	Ala	Leu	Glu	Arg	Leu	Thr	Lys	Ser	Ser	Glu	Ile
				740					745					750		
30	Arg	His	Gln	Gln	Ser	Ala	Glu	Phe	Val	Asn	Asp	Leu	Lys	Arg	Ala	Asn
			755					760					765			
	Ser	Asn	Leu	Val	Ala	Ala	Tyr	Glu	Lys	Ala	Lys	Lys	Lys	His	Gln	Asn
35		770					775					780				
	Lys	Leu	Lys	Lys	Leu	Glu	Ser	Gln	Met	Met	Ala	Met	Val	Glu	Arg	His
	785					790					795					800
40	Glu	Thr	Gln	Val	Arg	Met	Leu	Lys	Gln	Arg	Ile	Ala	Leu	Leu	Glu	Glu
					805					810					815	
	Glu	Asn	Ser	Arg	Pro	His	Thr	Asn	Glu	Thr	Ser	Leu				
45				820					825							

(2) INFORMATION FOR SEQ ID NO:27:

50	(i) SEQUENCE CHARACTERISTICS:
	(A) LENGTH: 672 amino acids
	(B) TYPE: amino acid
	(C) STRANDEDNESS: single
	(D) TOPOLOGY: linear
55	(ii) MOLECULE TYPE: peptide
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:27:
60	Met Ala Asp Val Phe Pro Gly Asn Asp Ser Thr Ala Ser Gln Asp Val
	1 5 10 15
	Ala Asn Arg Phe Ala Arg Lys Gly Ala Leu Arg Gln Lys Asn Val His
	20 25 30
65	Glu Val Lys Asp His Lys Phe Ile Ala Arg Phe Phe Lys Gln Pro Thr
	35 40 45

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Phe Cys Ser His Cys Thr Asp Phe Ile Trp Gly Phe Gly Lys Gly Gly
 50 55 60
 5 Phe Gln Cys Gln Val Cys Cys Phe Val Val His Lys Arg Cys His Glu
 65 70 75 80
 Phe Val Thr Phe Ser Cys Pro Gly Ala Asp Lys Gly Pro Asp Thr Asp
 85 90 95
 10 Asp Pro Arg Ser Lys His Lys Phe Lys Ile His Thr Tyr Gly Ser Pro
 100 105 110
 Thr Phe Cys Asp His Cys Gly Ser Leu Leu Tyr Gly Leu Ile His Gln
 115 120 125
 15 Gly Met Lys Cys Asp Thr Cys Asp Met Asn Val His Lys Gln Cys Val
 130 135 140
 Ile Asn Val Pro Ser Leu Cys Gly Met Asp His Thr Glu Lys Arg Gly
 145 150 155 160
 20 Arg Ile Tyr Leu Lys Ala Glu Val Ala Asp Glu Lys Leu His Val Thr
 165 170 175
 25 Val Arg Asp Ala Lys Asn Leu Ile Pro Met Asp Pro Asn Gly Leu Ser
 180 185 190
 Asp Pro Tyr Val Lys Leu Lys Leu Ile Pro Asp Pro Lys Asn Glu Ser
 195 200 205
 30 Lys Gln Lys Thr Lys Thr Ile Arg Ser Thr Leu Asn Pro Gln Trp Asn
 210 215 220
 Glu Ser Phe Thr Phe Lys Leu Lys Pro Ser Asp Lys Asp Arg Arg Leu
 225 230 235 240
 35 Ser Val Glu Ile Trp Asp Trp Asp Arg Thr Thr Arg Asn Asp Phe Met
 245 250 255
 40 Gly Ser Leu Ser Phe Gly Val Ser Glu Leu Met Lys Met Pro Ala Ser
 260 265 270
 Gly Trp Tyr Lys Leu Leu Asn Gln Glu Glu Gly Glu Tyr Tyr Asn Val
 275 280 285
 45 Pro Ile Pro Glu Gly Asp Glu Glu Gly Asn Met Glu Leu Arg Gln Lys
 290 295 300
 50 Phe Glu Lys Ala Lys Leu Gly Pro Ala Gly Asn Lys Val Ile Ser Pro
 305 310 315 320
 Ser Glu Asp Arg Lys Gln Pro Ser Asn Asn Leu Asp Arg Val Lys Leu
 325 330 335
 55 Thr Asp Phe Asn Phe Leu Met Val Leu Gly Lys Gly Ser Phe Gly Lys
 340 345 350
 Val Met Leu Ala Asp Arg Lys Gly Thr Glu Glu Leu Tyr Ala Ile Lys
 355 360 365
 60 Ile Leu Lys Lys Asp Val Val Ile Gln Asp Asp Asp Val Glu Cys Thr
 370 375 380
 65 Met Val Glu Lys Arg Val Leu Ala Leu Leu Asp Lys Pro Pro Phe Leu
 385 390 395 400
 Thr Gln Leu His Ser Cys Phe Gln Thr Val Asp Arg Leu Tyr Phe Val

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	405	410	415
	Met Glu Tyr Val Asn Gly Gly Asp Leu Met Tyr His Ile Gln Gln Val		
	420	425	430
5	Gly Lys Phe Lys Glu Pro Gln Ala Val Phe Tyr Ala Ala Glu Ile Ser		
	435	440	445
10	Ile Gly Leu Phe Phe Leu His Lys Arg Gly Ile Ile Tyr Arg Asp Leu		
	450	455	460
	Lys Leu Asp Asn Val Met Leu Asp Ser Glu Gly His Ile Lys Ile Ala		
	465	470	475
15	Asp Phe Gly Met Cys Lys Glu His Met Met Asp Gly Val Thr Thr Arg		
	485	490	495
	Thr Phe Cys Gly Thr Pro Asp Tyr Ile Ala Pro Glu Ile Ile Ala Tyr		
	500	505	510
20	Gln Pro Tyr Gly Lys Ser Val Asp Trp Trp Ala Tyr Gly Val Leu Leu		
	515	520	525
25	Tyr Glu Met Leu Ala Gly Gln Pro Pro Phe Asp Gly Glu Asp Glu Asp		
	530	535	540
	Glu Leu Phe Gln Ser Ile Met Glu His Asn Val Ser Tyr Pro Lys Ser		
	545	550	555
30	Leu Ser Lys Glu Ala Val Ser Ile Cys Lys Gly Leu Met Thr Lys His		
	565	570	575
	Pro Ala Lys Arg Leu Gly Cys Gly Pro Glu Gly Glu Arg Asp Val Arg		
	580	585	590
35	Glu His Ala Phe Phe Arg Arg Ile Asp Trp Glu Lys Leu Glu Asn Arg		
	595	600	605
40	Glu Ile Gln Pro Pro Phe Lys Pro Lys Val Cys Gly Lys Gly Ala Glu		
	610	615	620
	Asn Phe Asp Lys Phe Phe Thr Arg Gly Gln Pro Val Leu Thr Pro Pro		
	625	630	635
45	Asp Gln Leu Val Ile Ala Asn Ile Asp Gln Ser Asp Phe Glu Gly Phe		
	645	650	655
	Ser Tyr Val Asn Pro Gln Phe Val His Pro Ile Leu Gln Ser Ala Val		
	660	665	670

(2) INFORMATION FOR SEQ ID NO:28:

55 (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 471 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

60 (ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:28:

65	Met Asp Ile Leu Cys Glu Glu Asn Thr Ser Leu Ser Ser Thr Thr Asn
	1 5 10 15

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	Ser	Leu	Met	Gln	Leu	Asn	Asp	Asp	Thr	Arg	Leu	Tyr	Ser	Asn	Asp	Phe
				20					25					30		
5	Asn	Ser	Gly	Glu	Ala	Asn	Thr	Ser	Asp	Ala	Phe	Asn	Trp	Thr	Val	Asp
			35					40					45			
	Ser	Glu	Asn	Arg	Thr	Asn	Leu	Ser	Cys	Glu	Gly	Cys	Leu	Ser	Pro	Ser
		50					55					60				
10	Cys	Leu	Ser	Leu	Leu	His	Leu	Gln	Glu	Lys	Asn	Trp	Ser	Ala	Leu	Leu
	65					70					75					80
	Thr	Ala	Val	Val	Ile	Ile	Leu	Thr	Ile	Ala	Gly	Asn	Ile	Leu	Val	Ile
15					85					90					95	
	Met	Ala	Val	Ser	Leu	Glu	Lys	Lys	Leu	Gln	Asn	Ala	Thr	Asn	Tyr	Phe
				100					105					110		
20	Leu	Met	Ser	Leu	Ala	Ile	Ala	Asp	Met	Leu	Leu	Gly	Phe	Leu	Val	Met
			115					120					125			
	Pro	Val	Ser	Met	Leu	Thr	Ile	Leu	Tyr	Gly	Tyr	Arg	Trp	Pro	Leu	Pro
		130					135					140				
25	Ser	Lys	Leu	Cys	Ala	Val	Trp	Ile	Tyr	Leu	Asp	Val	Leu	Phe	Ser	Thr
	145					150					155					160
	Ala	Ser	Ile	Met	His	Leu	Cys	Ala	Ile	Ser	Leu	Asp	Arg	Tyr	Val	Ala
30					165					170					175	
	Ile	Gln	Asn	Pro	Ile	His	His	Ser	Arg	Phe	Asn	Ser	Arg	Thr	Lys	Ala
				180					185					190		
35	Phe	Leu	Lys	Ile	Ile	Ala	Val	Trp	Thr	Ile	Ser	Val	Gly	Ile	Ser	Met
			195					200					205			
	Pro	Ile	Pro	Val	Phe	Gly	Leu	Gln	Asp	Asp	Ser	Lys	Val	Phe	Lys	Glu
		210					215					220				
40	Gly	Ser	Cys	Leu	Leu	Ala	Asp	Asp	Asn	Phe	Val	Leu	Ile	Gly	Ser	Phe
	225					230					235					240
	Val	Ser	Phe	Phe	Ile	Pro	Leu	Thr	Ile	Met	Val	Ile	Thr	Tyr	Phe	Leu
45					245					250					255	
	Thr	Ile	Lys	Ser	Leu	Gln	Lys	Glu	Ala	Thr	Leu	Cys	Val	Ser	Asp	Leu
				260					265					270		
50	Gly	Thr	Arg	Ala	Lys	Leu	Ala	Ser	Phe	Ser	Phe	Leu	Pro	Gln	Ser	Ser
			275					280					285			
	Leu	Ser	Ser	Glu	Lys	Leu	Phe	Gln	Arg	Ser	Ile	His	Arg	Glu	Pro	Gly
		290					295					300				
55	Ser	Tyr	Thr	Gly	Arg	Arg	Thr	Met	Gln	Ser	Ile	Ser	Asn	Glu	Gln	Lys
	305					310					315					320
	Ala	Cys	Lys	Val	Leu	Gly	Ile	Val	Phe	Phe	Leu	Phe	Val	Val	Met	Trp
60					325					330					335	
	Cys	Pro	Phe	Phe	Ile	Thr	Asn	Ile	Met	Ala	Val	Ile	Cys	Lys	Glu	Ser
				340					345					350		
65	Cys	Asn	Glu	Asp	Val	Ile	Gly	Ala	Leu	Leu	Asn	Val	Phe	Val	Trp	Ile
		355						360					365			
	Gly	Tyr	Leu	Ser	Ser	Ala	Val	Asn	Pro	Leu	Val	Tyr	Thr	Leu	Phe	Asn

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	370		375		380
	Lys Thr Tyr Arg Ser Ala Phe Ser Arg Tyr Ile Gln Cys Gln Tyr Lys				
	385		390		395
5	Glu Asn Lys Lys Pro Leu Gln Leu Ile Leu Val Asn Thr Ile Pro Ala				
		405		410	415
10	Leu Ala Tyr Lys Ser Ser Gln Leu Gln Met Gly Gln Lys Lys Asn Ser		425		430
		420			
	Lys Gln Asp Ala Lys Thr Thr Asp Asn Asp Cys Ser Met Val Ala Leu		440		445
		435			
15	Gly Lys Gln His Ser Glu Glu Ala Ser Lys Asp Asn Ser Asp Gly Val		455		460
		450			
20	Asn Glu Lys Val Ser Cys Val		470		
	465				

(2) INFORMATION FOR SEQ ID NO:29:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 481 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:29:

35	Met Ala Leu Ser Tyr Arg Val Ser Glu Leu Gln Ser Thr Ile Pro Glu				
	1	5		10	15
	His Ile Leu Gln Ser Thr Phe Val His Val Ile Ser Ser Asn Trp Ser				
		20	25		30
40	Gly Leu Gln Thr Glu Ser Ile Pro Glu Glu Met Lys Gln Ile Val Glu				
		35	40	45	
	Glu Gln Gly Asn Lys Leu His Trp Ala Ala Leu Leu Ile Leu Met Val				
		50	55	60	
45	Ile Ile Pro Thr Ile Gly Gly Asn Thr Leu Val Ile Leu Ala Val Ser				
		65	70	75	80
50	Leu Glu Lys Lys Leu Gln Tyr Ala Thr Asn Tyr Phe Leu Met Ser Leu				
		85	90		95
	Ala Val Ala Asp Leu Leu Val Gly Leu Phe Val Met Pro Ile Ala Leu				
		100	105	110	
55	Leu Thr Ile Met Phe Glu Ala Met Trp Pro Leu Pro Leu Val Leu Cys				
		115	120	125	
	Pro Ala Trp Leu Phe Leu Asp Val Leu Phe Ser Thr Ala Ser Ile Met				
		130	135	140	
60	His Leu Cys Ala Ile Ser Val Asp Arg Tyr Ile Ala Ile Lys Lys Pro				
		145	150	155	160
65	Ile Gln Ala Asn Gln Tyr Asn Ser Arg Ala Thr Ala Phe Ile Lys Ile				
		165	170		175
	Thr Val Val Trp Leu Ile Ser Ile Gly Ile Ala Ile Pro Val Pro Ile				

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	180	185	190
	Lys Gly Ile Glu Thr Asp Val	Asp Asn Pro Asn Asn	Ile Thr Cys Val
	195	200	205
5	Leu Thr Lys Glu Arg Phe Gly	Asp Phe Met Leu Phe Gly	Ser Leu Ala
	210	215	220
10	Ala Phe Phe Thr Pro Leu Ala	Ile Met Ile Val Thr Tyr Phe	Leu Thr
	225	230	235
	Ile His Ala Leu Gln Lys Lys	Ala Tyr Leu Val Lys Asn	Lys Pro Pro
	245	250	255
15	Gln Arg Leu Thr Trp Leu Thr	Val Ser Thr Val Phe Gln	Arg Asp Glu
	260	265	270
	Thr Pro Cys Ser Ser Pro Glu	Lys Val Ala Met Leu Asp	Gly Ser Arg
	275	280	285
20	Lys Asp Lys Ala Leu Pro Asn	Ser Gly Asp Glu Thr Leu	Met Arg Arg
	290	295	300
25	Thr Ser Thr Ile Gly Lys Lys	Ser Val Gln Thr Ile Ser	Asn Glu Gln
	305	310	315
	Arg Ala Ser Lys Val Leu Gly	Ile Val Phe Phe Leu Phe	Leu Leu Met
	325	330	335
30	Trp Cys Pro Phe Phe Ile Thr	Asn Ile Thr Leu Val Leu	Cys Asp Ser
	340	345	350
	Cys Asn Gln Thr Thr Leu Gln	Met Leu Leu Glu Ile Phe	Val Trp Ile
	355	360	365
35	Gly Tyr Val Ser Ser Gly Val	Asn Pro Leu Val Tyr Thr	Leu Phe Asn
	370	375	380
40	Lys Thr Phe Arg Asp Ala Phe	Gly Arg Tyr Ile Thr Cys	Asn Tyr Arg
	385	390	395
	Ala Thr Lys Ser Val Lys Thr	Leu Arg Lys Arg Ser Ser	Lys Ile Tyr
	405	410	415
45	Phe Arg Asn Pro Met Ala Glu	Asn Ser Lys Phe Phe Lys	Lys His Gly
	420	425	430
	Ile Arg Asn Gly Ile Asn Pro	Ala Met Tyr Gln Ser Pro	Met Arg Leu
	435	440	445
50	Arg Ser Ser Thr Ile Gln Ser	Ser Ser Ile Ile Leu Leu	Asp Thr Leu
	450	455	460
55	Leu Leu Thr Glu Asn Glu Gly	Asp Lys Thr Glu Glu Gln	Val Ser Val
	465	470	475
	Val		

60 (2) INFORMATION FOR SEQ ID NO:30:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 2843 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

65

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(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:30:

5	Met	Ala	Ala	Ala	Ser	Tyr	Asp	Gln	Leu	Leu	Lys	Gln	Val	Glu	Ala	Leu	1	5	10	15
	Lys	Met	Glu	Asn	Ser	Asn	Leu	Arg	Gln	Glu	Leu	Glu	Asp	Asn	Ser	Asn	20	25	30	
10	His	Leu	Thr	Lys	Leu	Glu	Thr	Glu	Ala	Ser	Asn	Met	Lys	Glu	Val	Leu	35	40	45	
	Lys	Gln	Leu	Gln	Gly	Ser	Ile	Glu	Asp	Glu	Ala	Met	Ala	Ser	Ser	Gly	50	55	60	
15	Gln	Ile	Asp	Leu	Leu	Glu	Arg	Leu	Lys	Glu	Leu	Asn	Leu	Asp	Ser	Ser	65	70	75	80
	Asn	Phe	Pro	Gly	Val	Lys	Leu	Arg	Ser	Lys	Met	Ser	Leu	Arg	Ser	Tyr	85	90	95	
20	Gly	Ser	Arg	Glu	Gly	Ser	Val	Ser	Ser	Arg	Ser	Gly	Glu	Cys	Ser	Pro	100	105	110	
25	Val	Pro	Met	Gly	Ser	Phe	Pro	Arg	Arg	Gly	Phe	Val	Asn	Gly	Ser	Arg	115	120	125	
	Glu	Ser	Thr	Gly	Tyr	Leu	Glu	Glu	Leu	Glu	Lys	Glu	Arg	Ser	Leu	Leu	130	135	140	
30	Leu	Ala	Asp	Leu	Asp	Lys	Glu	Glu	Lys	Glu	Lys	Asp	Trp	Tyr	Tyr	Ala	145	150	155	160
	Gln	Leu	Gln	Asn	Leu	Thr	Lys	Arg	Ile	Asp	Ser	Leu	Pro	Leu	Thr	Glu	165	170	175	
35	Asn	Phe	Ser	Leu	Gln	Thr	Asp	Met	Thr	Arg	Arg	Gln	Leu	Glu	Tyr	Glu	180	185	190	
40	Ala	Arg	Gln	Ile	Arg	Val	Ala	Met	Glu	Glu	Gln	Leu	Gly	Thr	Cys	Gln	195	200	205	
	Asp	Met	Glu	Lys	Arg	Ala	Gln	Arg	Arg	Ile	Ala	Arg	Ile	Gln	Gln	Ile	210	215	220	
45	Glu	Lys	Asp	Ile	Leu	Arg	Ile	Arg	Gln	Leu	Leu	Gln	Ser	Gln	Ala	Thr	225	230	235	240
	Glu	Ala	Glu	Arg	Ser	Ser	Gln	Asn	Lys	His	Glu	Thr	Gly	Ser	His	Asp	245	250	255	
50	Ala	Glu	Arg	Gln	Asn	Glu	Gly	Gln	Gly	Val	Gly	Glu	Ile	Asn	Met	Ala	260	265	270	
55	Thr	Ser	Gly	Asn	Gly	Gln	Gly	Ser	Thr	Thr	Arg	Met	Asp	His	Glu	Thr	275	280	285	
	Ala	Ser	Val	Leu	Ser	Ser	Ser	Ser	Thr	His	Ser	Ala	Pro	Arg	Arg	Leu	290	295	300	
60	Thr	Ser	His	Leu	Gly	Thr	Lys	Val	Glu	Met	Val	Tyr	Ser	Leu	Leu	Ser	305	310	315	320
	Met	Leu	Gly	Thr	His	Asp	Lys	Asp	Asp	Met	Ser	Arg	Thr	Leu	Leu	Ala	325	330	335	

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	Met	Ser	Ser	Ser	Gln	Asp	Ser	Cys	Ile	Ser	Met	Arg	Gln	Ser	Gly	Cys	
				340					345					350			
5	Leu	Pro	Leu	Leu	Ile	Gln	Leu	Leu	His	Gly	Asn	Asp	Lys	Asp	Ser	Val	
			355					360					365				
	Leu	Leu	Gly	Asn	Ser	Arg	Gly	Ser	Lys	Glu	Ala	Arg	Ala	Arg	Ala	Ser	
		370					375					380					
10	Ala	Ala	Leu	His	Asn	Ile	Ile	His	Ser	Gln	Pro	Asp	Asp	Lys	Arg	Gly	
	385					390					395					400	
	Arg	Arg	Glu	Ile	Arg	Val	Leu	His	Leu	Leu	Glu	Gln	Ile	Arg	Ala	Tyr	
				405						410					415		
15	Cys	Ser	Thr	Cys	Trp	Glu	Trp	Gln	Glu	Ala	His	Glu	Pro	Gly	Met	Asp	
				420					425					430			
20	Gln	Asp	Lys	Asn	Pro	Met	Pro	Ala	Pro	Val	Glu	His	Gln	Ile	Cys	Pro	
			435					440					445				
	Ala	Val	Cys	Val	Leu	Met	Lys	Leu	Ser	Phe	Asp	Glu	Glu	His	Arg	His	
		450					455					460					
25	Ala	Met	Asn	Glu	Leu	Gly	Gly	Leu	Gln	Ala	Ile	Ala	Glu	Leu	Leu	Gln	
	465					470					475					480	
	Val	Asp	Cys	Glu	Met	Tyr	Gly	Leu	Thr	Asn	Asp	His	Tyr	Ser	Ile	Thr	
					485					490					495		
30	Leu	Arg	Arg	Tyr	Ala	Gly	Met	Ala	Leu	Thr	Asn	Leu	Thr	Phe	Gly	Asp	
				500					505					510			
	Val	Ala	Asn	Lys	Ala	Thr	Leu	Cys	Ser	Met	Lys	Gly	Cys	Met	Arg	Ala	
35				515				520					525				
	Leu	Val	Ala	Gln	Leu	Lys	Ser	Glu	Ser	Glu	Asp	Leu	Gln	Gln	Val	Ile	
		530					535					540					
40	Ala	Ser	Val	Leu	Arg	Asn	Leu	Ser	Trp	Arg	Ala	Asp	Val	Asn	Ser	Lys	
	545					550					555					560	
	Lys	Thr	Leu	Arg	Glu	Val	Gly	Ser	Val	Lys	Ala	Leu	Met	Glu	Cys	Ala	
					565					570					575		
45	Leu	Glu	Val	Lys	Lys	Glu	Ser	Thr	Leu	Lys	Ser	Val	Leu	Ser	Ala	Leu	
				580					585					590			
	Trp	Asn	Leu	Ser	Ala	His	Cys	Thr	Glu	Asn	Lys	Ala	Asp	Ile	Cys	Ala	
50			595					600					605				
	Val	Asp	Gly	Ala	Leu	Ala	Phe	Leu	Val	Gly	Thr	Leu	Thr	Tyr	Arg	Ser	
		610					615					620					
55	Gln	Thr	Asn	Thr	Leu	Ala	Ile	Ile	Glu	Ser	Gly	Gly	Gly	Ile	Leu	Arg	
	625					630					635					640	
	Asn	Val	Ser	Ser	Leu	Ile	Ala	Thr	Asn	Glu	Asp	His	Arg	Gln	Ile	Leu	
					645					650					655		
60	Arg	Glu	Asn	Asn	Cys	Leu	Gln	Thr	Leu	Leu	Gln	His	Leu	Lys	Ser	His	
				660					665					670			
	Ser	Leu	Thr	Ile	Val	Ser	Asn	Ala	Cys	Gly	Thr	Leu	Trp	Asn	Leu	Ser	
65			675					680					685				
	Ala	Arg	Asn	Pro	Lys	Asp	Gln	Glu	Ala	Leu	Trp	Asp	Met	Gly	Ala	Val	

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	690	695	700	
5	Ser 705	Met Leu Lys Asn Leu Ile His Ser Lys His Lys Met Ile Ala Met 720		
	Gly	Ser Ala Ala Ala Leu Arg Asn Leu Met Ala Asn Arg Pro Ala Lys 735		
10	Tyr	Lys Asp Ala Asn Ile Met Ser Pro Gly Ser Ser Leu Pro Ser Leu 740 745 750		
	His	Val Arg Lys Gln Lys Ala Leu Glu Ala Glu Leu Asp Ala Gln His 755 760 765		
15	Leu	Ser Glu Thr Phe Asp Asn Ile Asp Asn Ile Ser Pro Lys Ala Ser 770 775 780		
	His	Arg Ser Lys Gln Arg His Lys Gln Ser Leu Tyr Gly Asp Tyr Val 785 790 795 800		
20	Phe	Asp Thr Asn Arg His Asp Asp Asn Arg Ser Asp Asn Phe Asn Thr 805 810 815		
25	Gly	Asn Met Thr Val Leu Ser Pro Tyr Leu Asn Thr Thr Val Leu Pro 820 825 830		
	Ser	Ser Ser Ser Arg Gly Ser Leu Asp Ser Ser Arg Ser Glu Lys 835 840 845		
30	Asp	Arg Ser Leu Glu Arg Glu Arg Gly Ile Gly Leu Gly Asn Tyr His 850 855 860		
	Pro	Ala Thr Glu Asn Pro Gly Thr Ser Ser Lys Arg Gly Leu Gln Ile 865 870 875 880		
35	Ser	Thr Thr Ala Ala Gln Ile Ala Lys Val Met Glu Glu Val Ser Ala 885 890 895		
40	Ile	His Thr Ser Gln Glu Asp Arg Ser Ser Gly Ser Thr Thr Glu Leu 900 905 910		
	His	Cys Val Thr Asp Glu Arg Asn Ala Leu Arg Arg Ser Ser Ala Ala 915 920 925		
45	His	Thr His Ser Asn Thr Tyr Asn Phe Thr Lys Ser Glu Asn Ser Asn 930 935 940		
	Arg	Thr Cys Ser Met Pro Tyr Ala Lys Leu Glu Tyr Lys Arg Ser Ser 945 950 955 960		
50	Asn	Asp Ser Leu Asn Ser Val Ser Ser Ser Asp Gly Tyr Gly Lys Arg 965 970 975		
55	Gly	Gln Met Lys Pro Ser Ile Glu Ser Tyr Ser Glu Asp Asp Glu Ser 980 985 990		
	Lys	Phe Cys Ser Tyr Gly Gln Tyr Pro Ala Asp Leu Ala His Lys Ile 995 1000 1005		
60	His	Ser Ala Asn His Met Asp Asp Asn Asp Gly Glu Leu Asp Thr Pro 1010 1015 1020		
	Ile	Asn Tyr Ser Leu Lys Tyr Ser Asp Glu Gln Leu Asn Ser Gly Arg 1025 1030 1035 1040		
65	Gln	Ser Pro Ser Gln Asn Glu Arg Trp Ala Arg Pro Lys His Ile Ile 1045 1050 1055		

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	Glu Asp Glu Ile Lys Gln Ser Glu Gln Arg Gln Ser Arg Asn Gln Ser	1060	1065	1070
5	Thr Thr Tyr Pro Val Tyr Thr Glu Ser Thr Asp Asp Lys His Leu Lys	1075	1080	1085
	Phe Gln Pro His Phe Gly Gln Gln Glu Cys Val Ser Pro Tyr Arg Ser	1090	1095	1100
10	Arg Gly Ala Asn Gly Ser Glu Thr Asn Arg Val Gly Ser Asn His Gly	1105	1110	1115
	Ile Asn Gln Asn Val Ser Gln Ser Leu Cys Gln Glu Asp Asp Tyr Glu	1125	1130	1135
15	Asp Asp Lys Pro Thr Asn Tyr Ser Glu Arg Tyr Ser Glu Glu Gln	1140	1145	1150
	His Glu Glu Glu Glu Arg Pro Thr Asn Tyr Ser Ile Lys Tyr Asn Glu	1155	1160	1165
20	Glu Lys Arg His Val Asp Gln Pro Ile Asp Tyr Ser Ile Leu Lys Ala	1170	1175	1180
25	Thr Asp Ile Pro Ser Ser Gln Lys Gln Ser Phe Ser Phe Ser Lys Ser	1185	1190	1195
	Ser Ser Gly Gln Ser Ser Lys Thr Glu His Met Ser Ser Ser Ser Glu	1205	1210	1215
30	Asn Thr Ser Thr Pro Ser Ser Asn Ala Lys Arg Gln Asn Gln Leu His	1220	1225	1230
35	Pro Ser Ser Ala Gln Ser Arg Ser Gly Gln Pro Gln Lys Ala Ala Thr	1235	1240	1245
	Cys Lys Val Ser Ser Ile Asn Gln Glu Thr Ile Gln Thr Tyr Cys Val	1250	1255	1260
40	Glu Asp Thr Pro Ile Cys Phe Ser Arg Cys Ser Ser Leu Ser Ser Leu	1265	1270	1275
	Ser Ser Ala Glu Asp Glu Ile Gly Cys Asn Gln Thr Thr Gln Glu Ala	1285	1290	1295
45	Asp Ser Ala Asn Thr Leu Gln Ile Ala Glu Ile Lys Glu Lys Ile Gly	1300	1305	1310
50	Thr Arg Ser Ala Glu Asp Pro Val Ser Glu Val Pro Ala Val Ser Gln	1315	1320	1325
	His Pro Arg Thr Lys Ser Ser Arg Leu Gln Gly Ser Ser Leu Ser Ser	1330	1335	1340
55	Glu Ser Ala Arg His Lys Ala Val Glu Phe Ser Ser Gly Ala Lys Ser	1345	1350	1355
	Pro Ser Lys Ser Gly Ala Gln Thr Pro Lys Ser Pro Pro Glu His Tyr	1365	1370	1375
60	Val Gln Glu Thr Pro Leu Met Phe Ser Arg Cys Thr Ser Val Ser Ser	1380	1385	1390
65	Leu Asp Ser Phe Glu Ser Arg Ser Ile Ala Ser Ser Val Gln Ser Glu	1395	1400	1405
	Pro Cys Ser Gly Met Val Ser Gly Ile Ile Ser Pro Ser Asp Leu Pro			

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	1410	1415	1420	
5	Asp Ser Pro Gly Gln Thr Met Pro Pro Ser Arg Ser Lys Thr Pro Pro 1425 1430 1435 1440			
	Pro Pro Pro Gln Thr Ala Gln Thr Lys Arg Glu Val Pro Lys Asn Lys 1445 1450 1455			
10	Ala Pro Thr Ala Glu Lys Arg Glu Ser Gly Pro Lys Gln Ala Ala Val 1460 1465 1470			
	Asn Ala Ala Val Gln Arg Val Gln Val Leu Pro Asp Ala Asp Thr Leu 1475 1480 1485			
15	Leu His Phe Ala Thr Glu Ser Thr Pro Asp Gly Phe Ser Cys Ser Ser 1490 1495 1500			
	Ser Leu Ser Ala Leu Ser Leu Asp Glu Pro Phe Ile Gln Lys Asp Val 1505 1510 1515 1520			
20	Glu Leu Arg Ile Met Pro Pro Val Gln Glu Asn Asp Asn Gly Asn Glu 1525 1530 1535			
	Thr Glu Ser Glu Gln Pro Lys Glu Ser Asn Glu Asn Gln Glu Lys Glu 1540 1545 1550			
25	Ala Glu Lys Thr Ile Asp Ser Glu Lys Asp Leu Leu Asp Asp Ser Asp 1555 1560 1565			
	Asp Asp Asp Ile Glu Ile Leu Glu Glu Cys Ile Ile Ser Ala Met Pro 1570 1575 1580			
	Thr Lys Ser Ser Arg Lys Ala Lys Lys Pro Ala Gln Thr Ala Ser Lys 1585 1590 1595 1600			
35	Leu Pro Pro Pro Val Ala Arg Lys Pro Ser Gln Leu Pro Val Tyr Lys 1605 1610 1615			
	Leu Leu Pro Ser Gln Asn Arg Leu Gln Pro Gln Lys His Val Ser Phe 1620 1625 1630			
	Thr Pro Gly Asp Asp Met Pro Arg Val Tyr Cys Val Glu Gly Thr Pro 1635 1640 1645			
45	Ile Asn Phe Ser Thr Ala Thr Ser Leu Ser Asp Leu Thr Ile Glu Ser 1650 1655 1660			
	Pro Pro Asn Glu Leu Ala Ala Gly Glu Gly Val Arg Gly Gly Ala Gln 1665 1670 1675 1680			
50	Ser Gly Glu Phe Glu Lys Arg Asp Thr Ile Pro Thr Glu Gly Arg Ser 1685 1690 1695			
	Thr Asp Glu Ala Gln Gly Gly Lys Thr Ser Ser Val Thr Ile Pro Glu 1700 1705 1710			
	Leu Asp Asp Asn Lys Ala Glu Glu Gly Asp Ile Leu Ala Glu Cys Ile 1715 1720 1725			
60	Asn Ser Ala Met Pro Lys Gly Lys Ser His Lys Pro Phe Arg Val Lys 1730 1735 1740			
	Lys Ile Met Asp Gln Val Gln Gln Ala Ser Ala Ser Ser Ser Ala Pro 1745 1750 1755 1760			
65	Asn Lys Asn Gln Leu Asp Gly Lys Lys Lys Lys Pro Thr Ser Pro Val 1765 1770 1775			

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	Lys	Pro	Ile	Pro	Gln	Asn	Thr	Glu	Tyr	Arg	Thr	Arg	Val	Arg	Lys	Asn	
				1780					1785					1790			
5	Ala	Asp	Ser	Lys	Asn	Asn	Leu	Asn	Ala	Glu	Arg	Val	Phe	Ser	Asp	Asn	
			1795					1800					1805				
	Lys	Asp	Ser	Lys	Lys	Gln	Asn	Leu	Lys	Asn	Asn	Ser	Lys	Asp	Phe	Asn	
			1810				1815					1820					
10	Asp	Lys	Leu	Pro	Asn	Asn	Glu	Asp	Arg	Val	Arg	Gly	Ser	Phe	Ala	Phe	
			1825			1830					1835					1840	
	Asp	Ser	Pro	His	His	Tyr	Thr	Pro	Ile	Glu	Gly	Thr	Pro	Tyr	Cys	Phe	
				1845						1850					1855		
15	Ser	Arg	Asn	Asp	Ser	Leu	Ser	Ser	Leu	Asp	Phe	Asp	Asp	Asp	Asp	Val	
				1860					1865					1870			
	Asp	Leu	Ser	Arg	Glu	Lys	Ala	Glu	Leu	Arg	Lys	Ala	Lys	Glu	Asn	Lys	
20			1875					1880					1885				
	Glu	Ser	Glu	Ala	Lys	Val	Thr	Ser	His	Thr	Glu	Leu	Thr	Ser	Asn	Gln	
			1890				1895					1900					
25	Gln	Ser	Ala	Asn	Lys	Thr	Gln	Ala	Ile	Ala	Lys	Gln	Pro	Ile	Asn	Arg	
			1905			1910					1915					1920	
	Gly	Gln	Pro	Lys	Pro	Ile	Leu	Gln	Lys	Gln	Ser	Thr	Phe	Pro	Gln	Ser	
				1925						1930					1935		
30	Ser	Lys	Asp	Ile	Pro	Asp	Arg	Gly	Ala	Ala	Thr	Asp	Glu	Lys	Leu	Gln	
				1940					1945					1950			
	Asn	Phe	Ala	Ile	Glu	Asn	Thr	Pro	Val	Cys	Phe	Ser	His	Asn	Ser	Ser	
35			1955					1960					1965				
	Leu	Ser	Ser	Leu	Ser	Asp	Ile	Asp	Gln	Glu	Asn	Asn	Asn	Lys	Glu	Asn	
			1970				1975					1980					
40	Glu	Pro	Ile	Lys	Glu	Thr	Glu	Pro	Pro	Asp	Ser	Gln	Gly	Glu	Pro	Ser	
			1985			1990					1995					2000	
	Lys	Pro	Gln	Ala	Ser	Gly	Tyr	Ala	Pro	Lys	Ser	Phe	His	Val	Glu	Asp	
				2005						2010					2015		
45	Thr	Pro	Val	Cys	Phe	Ser	Arg	Asn	Ser	Ser	Leu	Ser	Ser	Leu	Ser	Ile	
				2020					2025					2030			
	Asp	Ser	Glu	Asp	Asp	Leu	Leu	Gln	Glu	Cys	Ile	Ser	Ser	Ala	Met	Pro	
50			2035					2040					2045				
	Lys	Lys	Lys	Lys	Pro	Ser	Arg	Leu	Lys	Gly	Asp	Asn	Glu	Lys	His	Ser	
			2050				2055					2060					
55	Pro	Arg	Asn	Met	Gly	Gly	Ile	Leu	Gly	Glu	Asp	Leu	Thr	Leu	Asp	Leu	
			2065			2070					2075					2080	
	Lys	Asp	Ile	Gln	Arg	Pro	Asp	Ser	Glu	His	Gly	Leu	Ser	Pro	Asp	Ser	
				2085						2090					2095		
60	Glu	Asn	Phe	Asp	Trp	Lys	Ala	Ile	Gln	Glu	Gly	Ala	Asn	Ser	Ile	Val	
				2100					2105				2110				
	Ser	Ser	Leu	His	Gln	Ala	Ala	Ala	Ala	Ala	Cys	Leu	Ser	Arg	Gln	Ala	
65			2115				2120					2125					
	Ser	Ser	Asp	Ser	Asp	Ser	Ile	Leu	Ser	Leu	Lys	Ser	Gly	Ile	Ser	Leu	

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	2130	2135	2140
5	Gly Ser Pro Phe His Leu Thr Pro Asp Gln Glu Glu Lys Pro Phe Thr 2145 2150 2155 2160		
	Ser Asn Lys Gly Pro Arg Ile Leu Lys Pro Gly Glu Lys Ser Thr Leu 2165 2170 2175		
10	Glu Thr Lys Lys Ile Glu Ser Glu Ser Lys Gly Ile Lys Gly Gly Lys 2180 2185 2190		
	Lys Val Tyr Lys Ser Leu Ile Thr Gly Lys Val Arg Ser Asn Ser Glu 2195 2200 2205		
15	Ile Ser Gly Gln Met Lys Gln Pro Leu Gln Ala Asn Met Pro Ser Ile 2210 2215 2220		
	Ser Arg Gly Arg Thr Met Ile His Ile Pro Gly Val Arg Asn Ser Ser 2225 2230 2235 2240		
20	Ser Ser Thr Ser Pro Val Ser Lys Lys Gly Pro Pro Leu Lys Thr Pro 2245 2250 2255		
25	Ala Ser Lys Ser Pro Ser Glu Gly Gln Thr Ala Thr Thr Ser Pro Arg 2260 2265 2270		
	Gly Ala Lys Pro Ser Val Lys Ser Glu Leu Ser Pro Val Ala Arg Gln 2275 2280 2285		
30	Thr Ser Gln Ile Gly Gly Ser Ser Lys Ala Pro Ser Arg Ser Gly Ser 2290 2295 2300		
	Arg Asp Ser Thr Pro Ser Arg Pro Ala Gln Gln Pro Leu Ser Arg Pro 2305 2310 2315 2320		
35	Ile Gln Ser Pro Gly Arg Asn Ser Ile Ser Pro Gly Arg Asn Gly Ile 2325 2330 2335		
40	Ser Pro Pro Asn Lys Ile Ser Gln Leu Pro Arg Thr Ser Ser Pro Ser 2340 2345 2350		
	Thr Ala Ser Thr Lys Ser Ser Gly Ser Gly Lys Met Ser Tyr Thr Ser 2355 2360 2365		
45	Pro Gly Arg Gln Met Ser Gln Gln Asn Leu Thr Lys Gln Thr Gly Leu 2370 2375 2380		
	Ser Lys Asn Ala Ser Ser Ile Pro Arg Ser Glu Ser Ala Ser Lys Gly 2385 2390 2395 2400		
50	Leu Asn Gln Met Asn Asn Gly Asn Gly Ala Asn Lys Lys Val Glu Leu 2405 2410 2415		
55	Ser Arg Met Ser Ser Thr Lys Ser Ser Gly Ser Glu Ser Asp Arg Ser 2420 2425 2430		
	Glu Arg Pro Val Leu Val Arg Gln Ser Thr Phe Ile Lys Glu Ala Pro 2435 2440 2445		
60	Ser Pro Thr Leu Arg Arg Lys Leu Glu Glu Ser Ala Ser Phe Glu Ser 2450 2455 2460		
	Leu Ser Pro Ser Ser Arg Pro Ala Ser Pro Thr Arg Ser Gln Ala Gln 2465 2470 2475 2480		
65	Thr Pro Val Leu Ser Pro Ser Leu Pro Asp Met Ser Leu Ser Thr His 2485 2490 2495		

	Ser	Ser	Val	Gln	Ala	Gly	Gly	Trp	Arg	Lys	Leu	Pro	Pro	Asn	Leu	Ser	
					2500					2505					2510		
5	Pro	Thr	Ile	Glu	Tyr	Asn	Asp	Gly	Arg	Pro	Ala	Lys	Arg	His	Asp	Ile	
			2515					2520					2525				
	Ala	Arg	Ser	His	Ser	Glu	Ser	Pro	Ser	Arg	Leu	Pro	Ile	Asn	Arg	Ser	
		2530					2535					2540					
10	Gly	Thr	Trp	Lys	Arg	Glu	His	Ser	Lys	His	Ser	Ser	Ser	Leu	Pro	Arg	
	2545					2550					2555					2560	
	Val	Ser	Thr	Trp	Arg	Arg	Thr	Gly	Ser	Ser	Ser	Ser	Ile	Leu	Ser	Ala	
					2565					2570					2575		
15	Ser	Ser	Glu	Ser	Ser	Glu	Lys	Ala	Lys	Ser	Glu	Asp	Glu	Lys	His	Val	
			2580						2585					2590			
20	Asn	Ser	Ile	Ser	Gly	Thr	Lys	Gln	Ser	Lys	Glu	Asn	Gln	Val	Ser	Ala	
		2595						2600					2605				
	Lys	Gly	Thr	Trp	Arg	Lys	Ile	Lys	Glu	Asn	Glu	Phe	Ser	Pro	Thr	Asn	
		2610					2615					2620					
25	Ser	Thr	Ser	Gln	Thr	Val	Ser	Ser	Gly	Ala	Thr	Asn	Gly	Ala	Glu	Ser	
	2625					2630					2635					2640	
	Lys	Thr	Leu	Ile	Tyr	Gln	Met	Ala	Pro	Ala	Val	Ser	Lys	Thr	Glu	Asp	
					2645					2650					2655		
30	Val	Trp	Val	Arg	Ile	Glu	Asp	Cys	Pro	Ile	Asn	Asn	Pro	Arg	Ser	Gly	
				2660					2665					2670			
35	Arg	Ser	Pro	Thr	Gly	Asn	Thr	Pro	Pro	Val	Ile	Asp	Ser	Val	Ser	Glu	
			2675					2680					2685				
	Lys	Ala	Asn	Pro	Asn	Ile	Lys	Asp	Ser	Lys	Asp	Asn	Gln	Ala	Lys	Gln	
		2690					2695					2700					
40	Asn	Val	Gly	Asn	Gly	Ser	Val	Pro	Met	Arg	Thr	Val	Gly	Leu	Glu	Asn	
	2705					2710					2715					2720	
	Arg	Leu	Asn	Ser	Phe	Ile	Gln	Val	Asp	Ala	Pro	Asp	Gln	Lys	Gly	Thr	
					2725					2730					2735		
45	Glu	Ile	Lys	Pro	Gly	Gln	Asn	Asn	Pro	Val	Pro	Val	Ser	Glu	Thr	Asn	
				2740					2745					2750			
50	Glu	Ser	Ser	Ile	Val	Glu	Arg	Thr	Pro	Phe	Ser	Ser	Ser	Ser	Ser	Ser	
			2755					2760					2765				
	Lys	His	Ser	Ser	Pro	Ser	Gly	Thr	Val	Ala	Ala	Arg	Val	Thr	Pro	Phe	
		2770					2775					2780					
55	Asn	Tyr	Asn	Pro	Ser	Pro	Arg	Lys	Ser	Ser	Ala	Asp	Ser	Thr	Ser	Ala	
	2785					2790					2795					2800	
	Arg	Pro	Ser	Gln	Ile	Pro	Thr	Pro	Val	Asn	Asn	Asn	Thr	Lys	Lys	Arg	

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(2) INFORMATION FOR SEQ ID NO:31:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 65 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:31:

CGGAATTCNN NNNNNNNNAAC AGCNNNNNNN NNAATGAANN NCAAGTCTG NNNTGAGGAT 60
CCTCA 65

(2) INFORMATION FOR SEQ ID NO:32:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 65 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:32:

CGGAATTCGA CTCAGAANNN NNNAACTTCA GANNNNNNNAT CNNNNNNNNN GTCTGAGGAT 60
CCTCA 65

(2) INFORMATION FOR SEQ ID NO:33:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 65 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:33:

CGGAATTCNN NNNNNNNNNN NNNNNNNNNN NNNNNNNNNN NNNNNNNNNN NNNTGAGGAT 60
CCTCA 65

What is claimed is:

- 5 1. A composition capable of inhibiting specific binding
 between a signal-transducing protein and a
 cytoplasmic protein containing the amino acid
 sequence (G/S/A/E)-L-G-(F/I/L), wherein each -
~~represents a peptide bond, each parenthesis encloses~~
 amino acids which are alternatives to one other, and
10 each slash within such parentheses separating the
 alternative amino acids.
2. The composition of claim 1, wherein the cytoplasmic
 protein contains the amino acid sequence (K/R/Q)-X_n-
15 (G/S/A/E)-L-G-(F/I/L), wherein X represents any
 amino acid which is selected from the group
 comprising the twenty naturally occurring amino
 acids and n represents at least 2, but not more than
 4.
- 20 3. The composition of claim 1, wherein the cytoplasmic
 protein contains the amino acid sequence SLGI.
4. The composition of claim 1, wherein the signal-
25 transducing protein has at its carboxyl terminus the
 amino acid sequence (S/T)-X-(V/I/L), wherein each -
 represents a peptide bond, each parenthesis encloses
 amino acids which are alternatives to one other,
 each slash within such parentheses separating the
30 alternative amino acids, and the X represents any
 amino acid which is selected from the group
 comprising the twenty naturally occurring amino
 acids.
- 35 5. The composition of claim 1, wherein the composition
 comprises an antibody, an inorganic compound, an
 organic compound, a peptide, a peptidomimetic

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compound, a polypeptide, or a protein.

- 5 6. The composition of claim 5, wherein the peptide
 comprises the sequence (S/T)-X-(V/I/L)-COOH, wherein
 each - represents a peptide bond, each parenthesis
 encloses amino acids which are alternatives to one
 other, each slash within such parentheses separating
10 the alternative amino acids, the X represents any
 amino acid which is selected from the group
 comprising the twenty naturally occurring amino
 acids.
- 15 7. The composition of claim 6, wherein the peptide has
 the amino acid sequence DSENSNFRNEIQSLV.
8. The composition of claim 6, wherein the peptide has
 the amino acid sequence RNEIQSLV.
- 20 9. The composition of claim 6, wherein the peptide has
 the amino acid sequence NEIQSLV.
10. The composition of claim 6, wherein the peptide has
 the amino acid sequence EIQSLV.
- 25 11. The composition of claim 6, wherein the peptide has
 the amino acid sequence IQSLV.
12. The composition of claim 6, wherein the peptide has
 the amino acid sequence QSLV.
- 30 13. The composition of claim 6, wherein the peptide has
 the amino acid sequence SLV.
14. The composition of claim 6, wherein the peptide has
35 the amino acid sequence IPPDSEDGNEEQSLV.
15. The composition of claim 6, wherein the peptide has

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the amino acid sequence DSEMYNFRSQLASVV.

5

16. The composition of claim 6, wherein the peptide has the amino acid sequence IDLASEFLFLSNSFL.

17. The composition of claim 6, wherein the peptide has the amino acid sequence PPTCSQANSGRISTL.

10

18. The composition of claim 6, wherein the peptide has the amino acid sequence SDSNMNMNELSEV.

19. The composition of claim 6, wherein the peptide has the amino acid sequence QNFRTYIVSFV.

15

20. The composition of claim 6, wherein the peptide has the amino acid sequence RETIESTV.

21. The composition of claim 6, wherein the peptide has the amino acid sequence RGFISSLV.

20

22. The composition of claim 6, wherein the peptide has the amino acid sequence TIQSVI.

23. The composition of claim 6, wherein the peptide has the amino acid sequence ESLV.

25

24. The composition of claim 6, wherein the organic compound has the sequence Ac-SLV-COOH, wherein the Ac represents an acetyl, each - represent a peptide bond.

30

25. A composition capable of inhibiting specific binding between a signal-transducing protein having at its carboxyl terminus the amino acid sequence (S/T)-X-(V/I/L), wherein each - represents a peptide bond, each parenthesis encloses amino acids which are alternatives to one other, each slash within such

35

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parentheses separating the alternative amino acids, the X represents any amino acid which is selected from the group comprising the twenty naturally occurring amino acids, and a cytoplasmic protein.

5

26. The composition of claim 25, wherein the composition comprises an antibody, an inorganic compound, an organic compound, a peptide, a peptidomimetic compound, a polypeptide or a protein.

10

27. A method of identifying a compound capable of inhibiting specific binding between a signal-transducing protein and a cytoplasmic protein containing the amino acid sequence (G/S/A/E)-L-G-(F/I/L), wherein each - represents a peptide bond, each parenthesis encloses amino acids which are alternatives to one other, each slash within such parentheses separating the alternative amino acids, which comprises:

15

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- (a) contacting the cytoplasmic protein bound to the signal-transducing protein with a plurality of compounds under conditions permitting binding between a known compound previously shown to be able to displace the signal-transducing protein bound to the cytoplasmic protein and the bound cytoplasmic protein to form a complex; and

25

- (b) detecting the displaced signal-transducing protein or the complex formed in step (a), wherein the displacement indicates that the compound is capable of inhibiting specific binding between the signal-transducing protein and the cytoplasmic protein.

30

35

28. The method of claim 27, wherein the inhibition of specific binding between the signal-transducing

protein and the cytoplasmic protein affects the transcription activity of a reporter gene.

- 5 29. The method of claim 28, where in step (b) the displaced signal-transducing protein or the complex is detected by comparing the transcription activity of a reporter gene before and after the contacting with the compound in step (a), where a change of the activity indicates that the specific binding between
- 10 the signal-transducing protein and the cytoplasmic protein is inhibited and the signal-transducing protein is displaced.
- 15 30. The method of claim 27, wherein the cytoplasmic protein is bound to a solid support.
31. The method of claim 27, wherein the compound is bound to a solid support.
- 20 32. The method of claim 27, wherein the compound comprises an antibody, an inorganic compound, an organic compound, a peptide, a peptidomimetic compound, a polypeptide or a protein.
- 25 33. The method of claim 27, wherein the contacting of step (a) is in vitro.
34. The method of claim 27, wherein the contacting of step (a) is in vivo.
- 30 35. The method of claim 34, wherein the contacting of step (a) is in a yeast cell.
36. The method of claim 34, wherein the contacting or
- 35 step (a) is in a mammalian cell.
37. The method of claim 27, wherein the signal-

transducing protein is a cell surface receptor.

38. The method of claim 27, wherein the signal-transducing protein is a signal transducer protein.

39. The method of claim 27, wherein the signal-transducing protein is a tumor suppressor protein.

40. The method of claim 37, wherein the cell surface protein is the Fas receptor.

41. The method of claim 40, wherein the Fas receptor is expressed in cells derived from organs comprising the thymus, liver, kidney, colon, ovary, breast, testis, spleen, stomach, prostate, uterus, skin, head and neck.

42. The method of claim 40, wherein the Fas receptor is expressed in cells comprising T-cells and B-cells.

43. The method of claim 37, wherein the cell-surface receptor is the CD4 receptor.

44. The method of claim 37, wherein the cell-surface receptor is the p75 receptor.

45. The method of claim 37, wherein the cell-surface receptor is the serotonin 2A receptor.

46. The method of claim 37, wherein the cell-surface receptor is the serotonin 2B receptor.

47. The method of claim 38, wherein the signal transducer protein is Protein Kinase-C- α -type.

48. The method of claim 39, wherein the tumor suppressor protein is adenomatosis polyposis coli tumor

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suppressor protein.

49. The method of claim 39, wherein the tumor suppressor protein protein is the colorectal mutant cancer protein.

5

50. The method of claim 27, wherein the cytoplasmic protein contains the amino acid sequence SLGI, wherein each - represents a peptide bond, each parenthesis encloses amino acids which are alternatives to one other, and each slash within such parentheses separating the alternative amino acids.

10

51. The method of claim 40, wherein the cytoplasmic protein is Fas-associated phosphatase-1.

15

52. A method of identifying a compound capable of inhibiting specific binding between a signal-transducing protein having at its carboxyl terminus the amino acid sequence (S/T)-X-(V/I/L), wherein each - represents a peptide bond, each parenthesis encloses amino acids which are alternatives to one other, each slash within such parentheses separating the alternative amino acids, the X represents any amino acid which is selected from the group comprising the twenty naturally occurring amino acids, and a cytoplasmic protein, which comprises:

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(a) contacting the signal-transducing protein bound to the cytoplasmic protein with a plurality of compounds under conditions permitting binding between a known compound previously shown to be able to displace the cytoplasmic protein bound to the signal-transducing protein and the bound signal-transducing protein to form a complex; and

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(b) detecting the displaced cytoplasmic protein or the complex of step (a) wherein the displacement indicates that the compound is capable of inhibiting specific binding between the signal-transducing protein and the cytoplasmic protein.

53. The method of claim 52, wherein the inhibition of specific binding between the signal-transducing protein and the cytoplasmic protein affects the transcription activity of a reporter gene.

54. The method of claim 53, where in step (b) the displaced cytoplasmic protein or the complex is detected by comparing the transcription activity of a reporter gene before and after the contacting with the compound in step (a), where a change of the activity indicates that the specific binding between the signal-transducing protein and the cytoplasmic protein is inhibited and the cytoplasmic protein is displaced.

55. The method of claim 52, wherein the cytoplasmic protein is bound to a solid support.

56. The method of claim 52, wherein the compound is bound to a solid support.

57. The method of claim 52, wherein the compound comprises an antibody, an inorganic compound, an organic compound, a peptide, a peptidomimetic compound, a polypeptide or a protein.

58. The method of claim 52, wherein the contacting of step (a) is in vitro.

59. The method of claim 52, wherein the contacting of

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step (a) is in vivo.

60. The method of claim 59, wherein the contacting of step (a) is in a yeast cell.

61. The method of claim 59, wherein the contacting or step (a) is in a mammalian cell.

62. The method of claim 52, wherein the signal-transducing protein is a cell surface receptor.

63. The method of claim 52, wherein the signal-transducing protein is a signal transducer protein.

64. The method of claim 52, wherein the signal-transducing protein is a tumor suppressor protein.

65. The method of claim 62, wherein the cell surface protein is the Fas receptor.

66. The method of claim 65, wherein the Fas receptor is expressed in cells derived from organs comprising the thymus, liver, kidney, colon, ovary, breast, testis, spleen, stomach, prostate, uterus, skin, head and neck.

67. The method of claim 65, wherein the Fas receptor is expressed in cells comprising T-cells and B-cells.

68. The method of claim 62, wherein the cell-surface receptor is the CD4 receptor.

69. The method of claim 62, wherein the cell-surface receptor is the p75 receptor.

70. The method of claim 62, wherein the cell-surface receptor is the serotonin 2A receptor.

71. The method of claim 62, wherein the cell-surface receptor is the serotonin 2B receptor.

5 72. The method of claim 63, wherein the signal transducer protein is Protein Kinase-C- α -type.

73. The method of claim 64, wherein the tumor suppressor protein is adenomatosis polyposis coli tumor
10 suppressor protein.

74. The method of claim 64, wherein the tumor suppressor protein is the colorectal mutant cancer protein.

15 75. The method of claim 52, wherein the cytoplasmic protein contains the amino acid sequence SLGI, wherein each - represents a peptide bond, each parenthesis encloses amino acids which are alternatives to one other, and each slash within
20 such parentheses separating the alternative amino acids.

76. The method of claim 52, wherein the cytoplasmic protein is Fas-associated phosphatase-1.
25

77. A method inhibiting the proliferation of cancer cells comprising the composition of claim 1.

78. The method of claim 77, wherein the cancer cells are derived from organs comprising the thymus, liver, kidney, colon, ovary, breast, testis, spleen, stomach, prostate, uterus, skin, head and neck.
30

79. The method of claim 77, wherein the cancer cells are derived from cells comprising T-cells and B-cells.
35

80. A method of inhibiting the proliferation of cancer

cells comprising the composition of claim 25.

- 5 81. The method of claim 80, wherein the cancer cells are derived from organs comprising the thymus, liver, kidney, colon, ovary, breast, testis, spleen, stomach, prostate, uterus, skin, head and neck.
- 10 82. The method of claim 80, wherein the cancer cells are derived from cells comprising T-cells and B-cells.
83. A method of inhibiting the proliferation of cancer cells comprising the compound identified by the method of claim 27.
- 15 84. The method of claim 83, wherein the cancer cells are derived from organs comprising the thymus, liver, kidney, colon, ovary, breast, testis, spleen, stomach, prostate, uterus, skin, head and neck.
- 20 85. The method of claim 83, wherein the cancer cells are derived from cells comprising T-cells and B-cells.
86. A method of inhibiting the proliferation of cancer cells comprising the compound identified by the method of claim 52.
- 25 87. The method of claim 86, wherein the cancer cells are derived from organs comprising the thymus, liver, kidney, colon, ovary, breast, testis, spleen, stomach, prostate, uterus, skin, head and neck.
- 30 88. The method of claim 86, wherein the cancer cells are derived from cells comprising T-cells and B-cells.
89. A method of treating cancer in a subject which comprises introducing to the subject's cancerous cells an amount of the composition of claim 1
- 35

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effective to result in apoptosis of the cells.

- 5 90. The method of claim 89, wherein the cancer cells are derived from organs comprising the thymus, liver, kidney, colon, ovary, breast, testis, spleen, stomach, prostate, uterus, skin, head and neck.
- 10 91. The method of claim 89, wherein the cancer cells are derived from cells comprising T-cells and B-cells.
- 15 92. A method of treating cancer in a subject which comprises introducing to the subject's cancerous cells an amount of the composition of claim 25 effective to result in apoptosis of the cells.
- 20 93. The method of claim 92, wherein the cancer cells are derived from organs comprising the thymus, liver, kidney, colon, ovary, breast, testis, spleen, stomach, prostate, uterus, skin, head and neck.
- 25 94. The method of claim 92, wherein the cancer cells are derived from cells comprising T-cells and B-cells.
95. A method of treating cancer in a subject which comprises introducing to the subject's cancerous cells an amount of the compound identified by the method of claim 27 effective to allow apoptosis of the cells.
- 30 96. The method of claim 95, wherein the cancer cells are derived from organs comprising the thymus, liver, kidney, colon, ovary, breast, testis, spleen, stomach, prostate, uterus, skin, head and neck.
- 35 97. The method of claim 95, wherein the cancer cells are derived from cells comprising T-cells and B-cells.

98. A method of treating cancer in a subject which comprises introducing to the subject's cancerous cells an amount of the compound identified by the method of claim 52 effective to result in apoptosis of the cells.

99. The method of claim 98, wherein the cancer cells are derived from organs comprising the thymus, liver, kidney, colon, ovary, breast, testis, spleen, stomach, prostate, uterus, skin, head and neck.

100. The method of claim 98, wherein the cancer cells are derived from cells comprising T-cells and B-cells.

101. A method of inhibiting the proliferation of virally infected cells comprising the composition of claim 1.

102. A method of inhibiting the proliferation of virally infected cells comprising the composition of claim 25.

103. A method of inhibiting the proliferation of virally infected cells comprising the compound identified by the method of claim 27.

104. A method of inhibiting the proliferation of virally infected cells comprising the compound identified by the method of claim 52.

105. The method of claim 101, wherein the virally infected cells comprise Hepatitis B virus, Epstein-Barr virus, influenza virus, Papilloma virus. Adeno virus, Human T-cell lymphotropic virus, type 1 or HIV.

106. The method of claim 102, wherein the virally

-75-

infected cells comprise Hepatitis B virus, Epstein-Barr virus, influenza virus, Papilloma virus. Adeno virus, Human T-cell lymphotropic virus, type 1 or HIV.

5

107. The method of claim 103, wherein the virally infected cells comprise Hepatitis B virus, Epstein-Barr virus, influenza virus, Papilloma virus. Adeno virus, Human T-cell lymphotropic virus, type 1 or HIV.

10

108. The method of claim 104, wherein the virally infected cells comprise Hepatitis B virus, Epstein-Barr virus, influenza virus, Papilloma virus. Adeno virus, Human T-cell lymphotropic virus, type 1 or HIV.

15

109. A method of treating a virally-infected subject which comprises introducing to the subject's virally- infected cells the composition of claim 1 effective to result in apoptosis of the cells.

20

110. A method of treating a virally-infected subject which comprises introducing to the subject's virally infected cells the composition of claim 25 effective to result in apoptosis of the cells.

25

111. A method of treating a virally-infected subject which comprises introducing to the subject's virally-infected cells an amount of the compound identified by the method of claim 27 effective to result in apoptosis of the cells.

30

112. A method of treating a virally-infected subject which comprises introducing to the subject's virally- infected cells an amount of the compound identified by the method of claim 52 effective to

35

result in apoptosis of the cells.

113. The method of claim 109, wherein the virally
5 infected cells comprise the Hepatitis B virus,
Epstein-Barr virus, influenza virus, Papilloma
virus. Adeno virus, Human T-cell lymphotropic virus,
type 1 or HIV.

114. The method of claim 110, wherein the virally
10 infected cells comprise the Hepatitis B virus,
Epstein-Barr virus, influenza virus, Papilloma
virus. Adeno virus, Human T-cell lymphotropic virus,
type 1 or HIV.

115. The method of claim 111, wherein the virally
15 infected cells comprise the Hepatitis B virus,
Epstein-Barr virus, influenza virus, Papilloma
virus. Adeno virus, Human T-cell lymphotropic virus,
type 1 or HIV.

116. The method of claim 112, wherein the virally
20 infected cells comprise the Hepatitis B virus,
Epstein-Barr virus, influenza virus, Papilloma
virus. Adeno virus, Human T-cell lymphotropic virus,
25 type 1 or HIV.

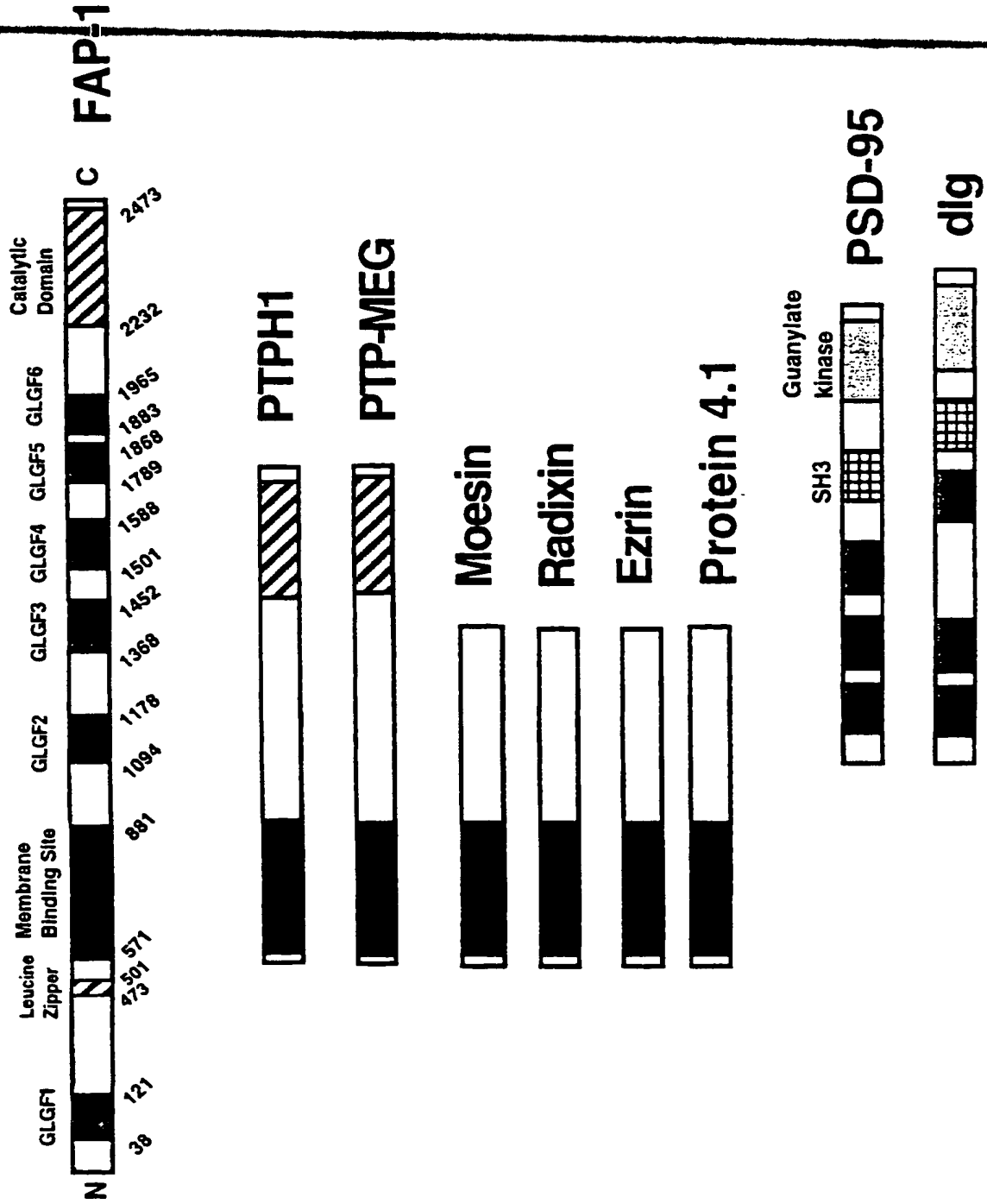
117. A pharmaceutical composition comprising the
composition of claim 1 in an effective amount and a
pharmaceutically acceptable carrier.

118. A pharmaceutical composition comprising the
composition of claim 25 in an effective amount and
a pharmaceutically acceptable carrier.

119. A pharmaceutical composition comprising the compound
35 identified by the method of claim 27 in an effective
amount and a pharmaceutically acceptable carrier.

120. A pharmaceutical composition comprising the compound identified by the method of claim 52 in an effective amount and a pharmaceutically acceptable carrier.

FIG. 1



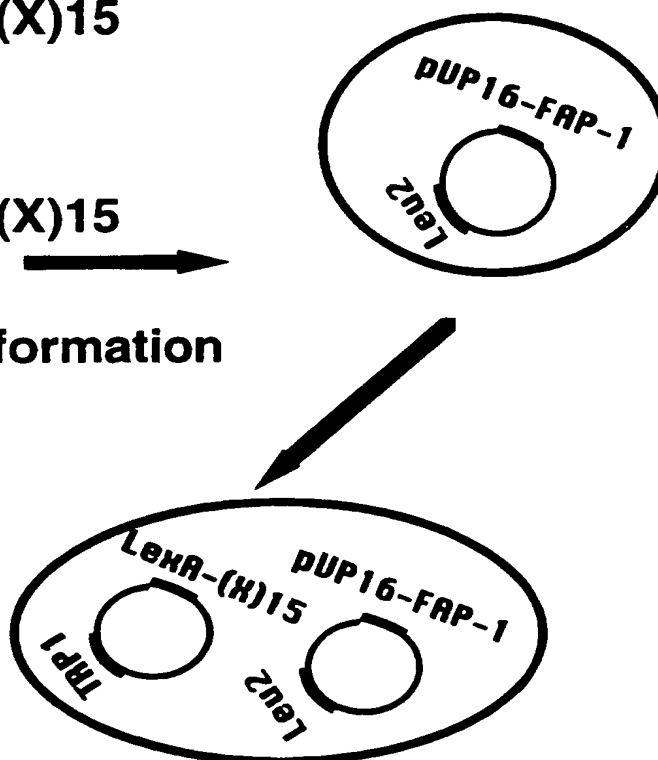
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FIG. 2A

Construction of
pBTM116 (LexA)-(X)15

Library DNAs of
pBTM116 (LexA)-(X)15

Large scale transformation
of yeast L40



His+, β -gal+

Curing of pVP16-FAP-1

Isolation of
pBTM116 (LexA)-(X)15

Analysis of
DNA sequences

FIG. 2B

Human	D	S	E	N	S	N	F	R	N	E	I	Q	S	L	V
Rat	S	I	S	N	S	R	N	E	N	E	G	Q	S	L	E
Mouse	S	T	P	D	T	G	N	E	N	E	G	Q	C	L	E

FIG. 2C

- - - N S - - - N E - Q S L -

C	Y	A		A	I	G		L							V	12-0
E	N	A		G	V	S		E							V	5-0
W	W	G		A	T	Q		P							V	13-0
E	H	A		Q	Q			Q							V	20-0
N	S	S		F	H	S		L							V	6-2
G	L	R		L	P	P		D							V	9-5
G	S	D		S	G	V		N							V	18-1
D	K	K		R	P	V		N							V	22-1
T	G	K		D	V	W		A							V	71-1
A	S	R		N	E	E		L							I	14-5

FIG. 2D

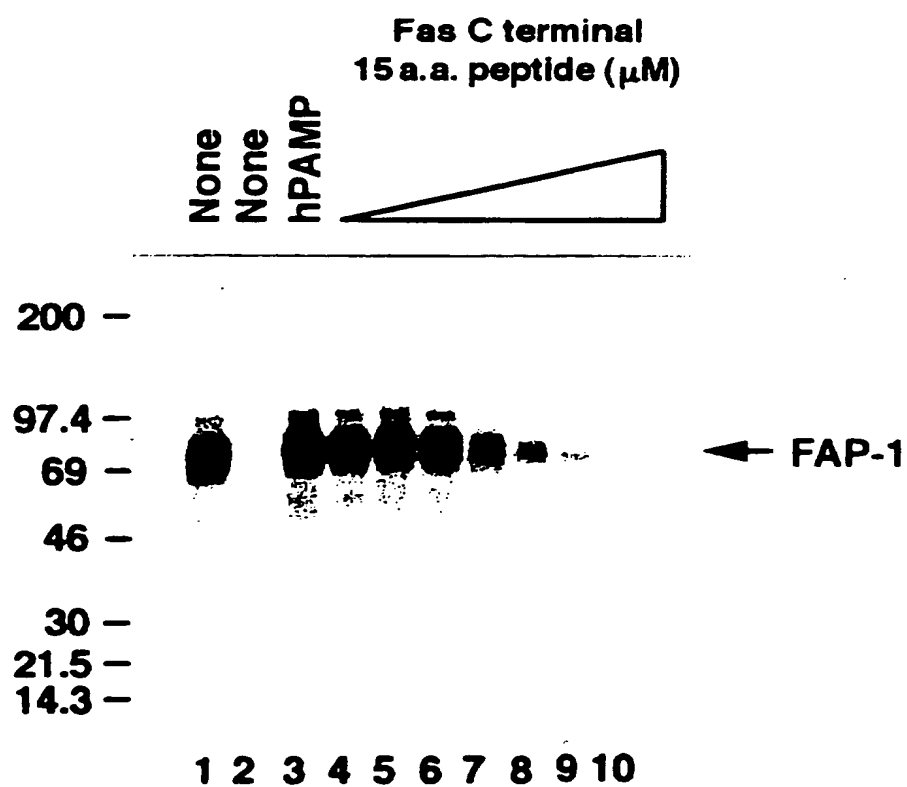
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I	P	D	S	E	D	G	N	E	E	Q	S	L	V	8-1	
D	S	E	M	Y	N	F	R	S	Q	L	A	S	V	9-3	
I	D	L	A	S	E	F	L	F	L	S	N	S	F	L	14-1
P	P	T	C	S	Q	A	N	S	G	R	I	S	T	L	0-2
S	D	S	N	M	N	M	N	E	L	S	E	V	57-5		
Q	N	F	R	T	Y	I	V	S	F	V	72-1				
R	E	T	I	E	S	T	V	25-9							
R	G	F	I	S	S	L	V	16-13							
T	I	Q	S	V	I	6-3									
E	S	L	V	18-1											

Consensus: t S-X-V/L/I

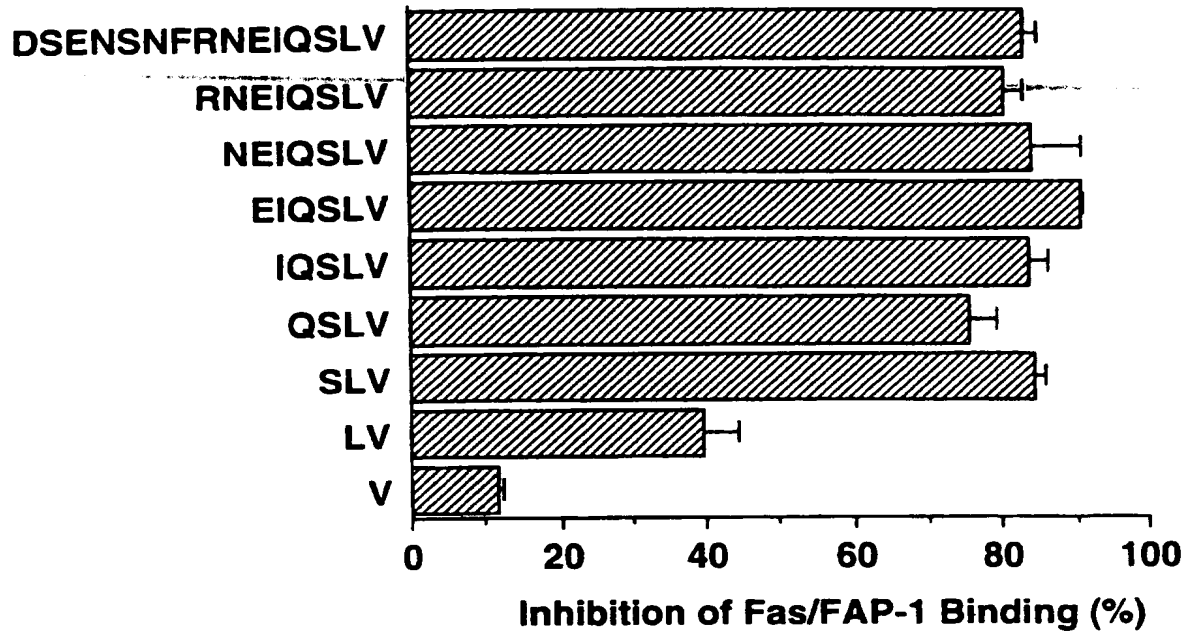
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FIG. 3A



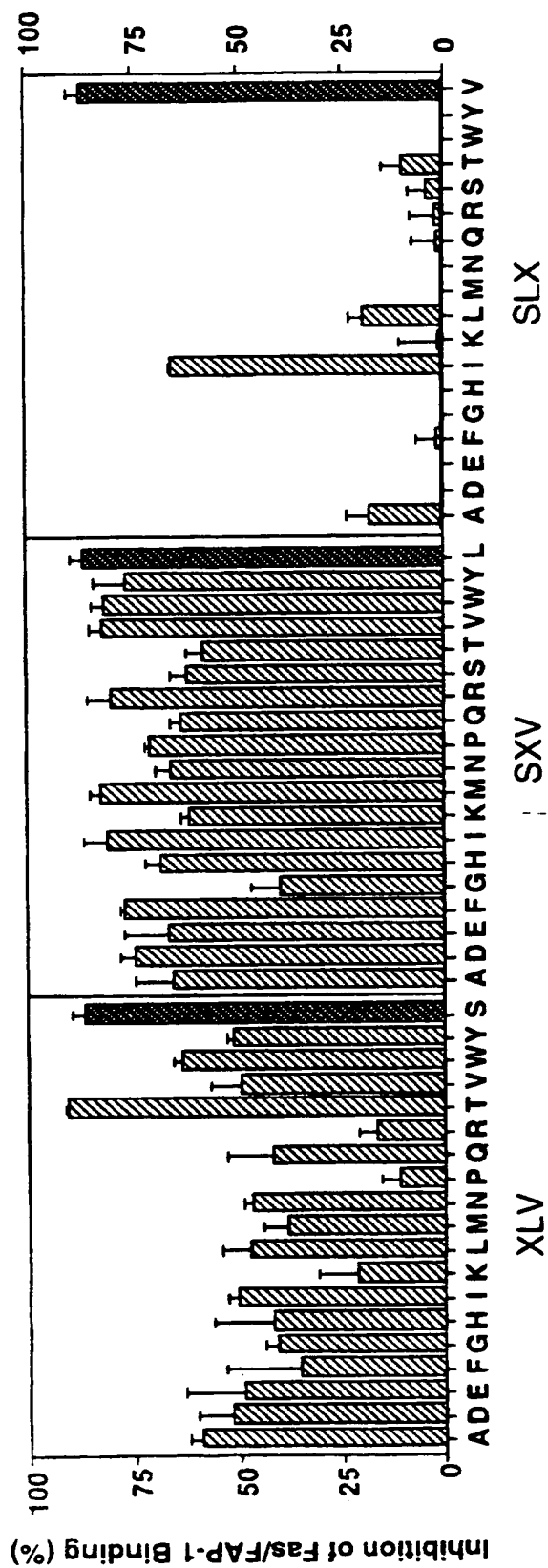
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FIG. 3B



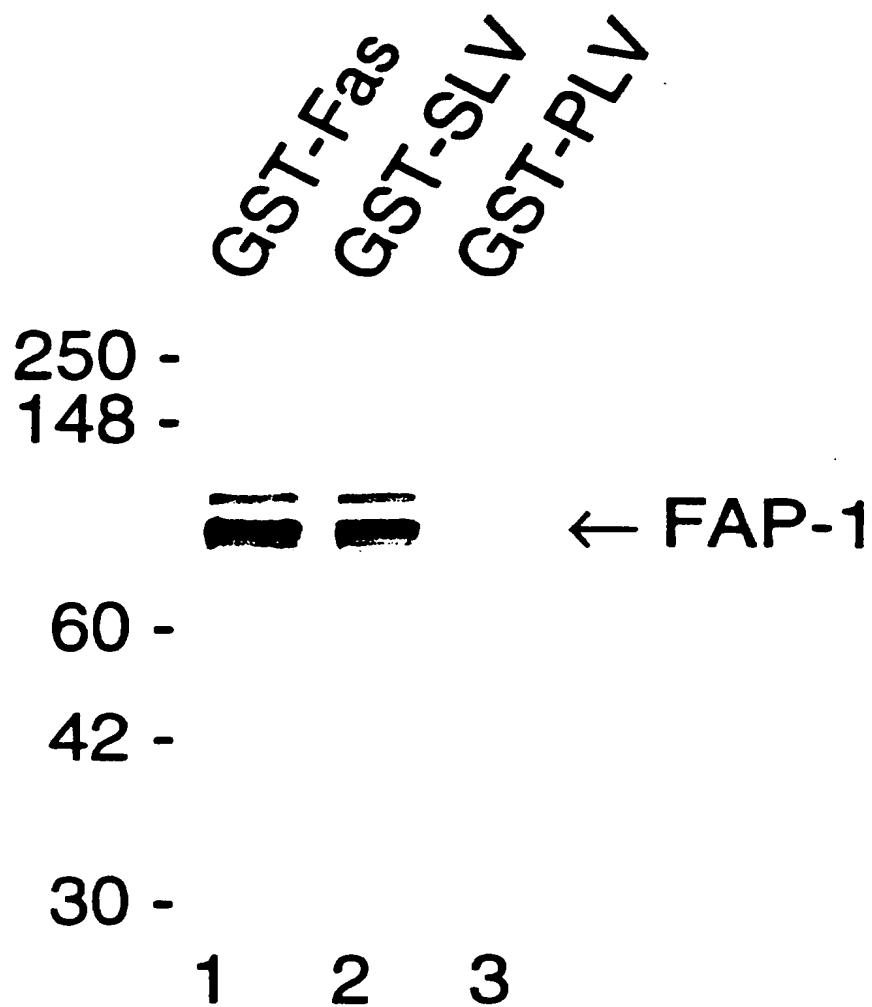
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FIG. 3C

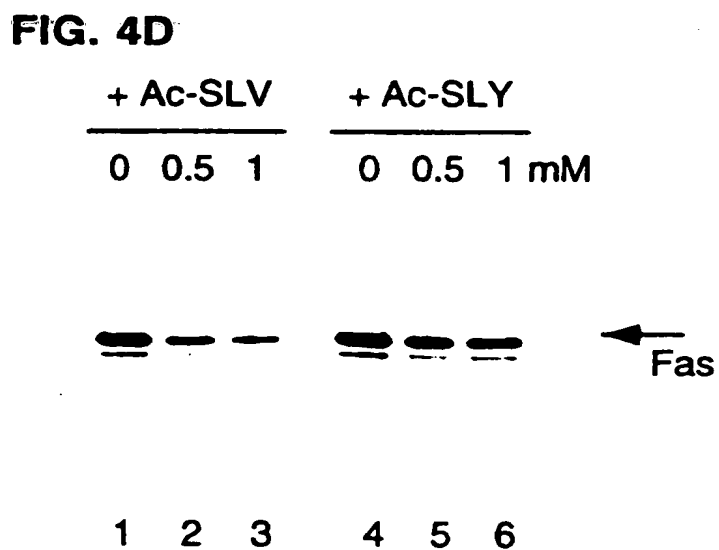
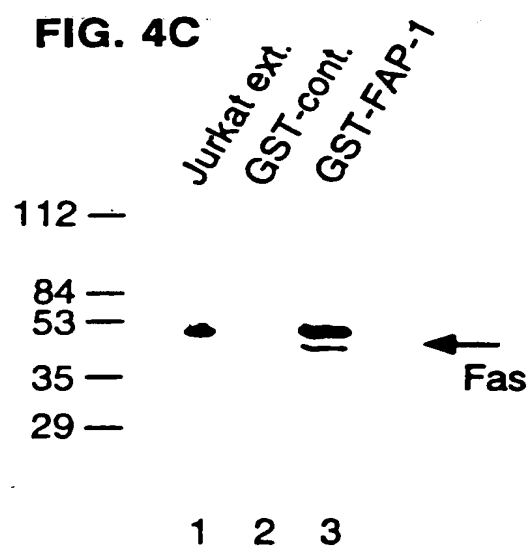


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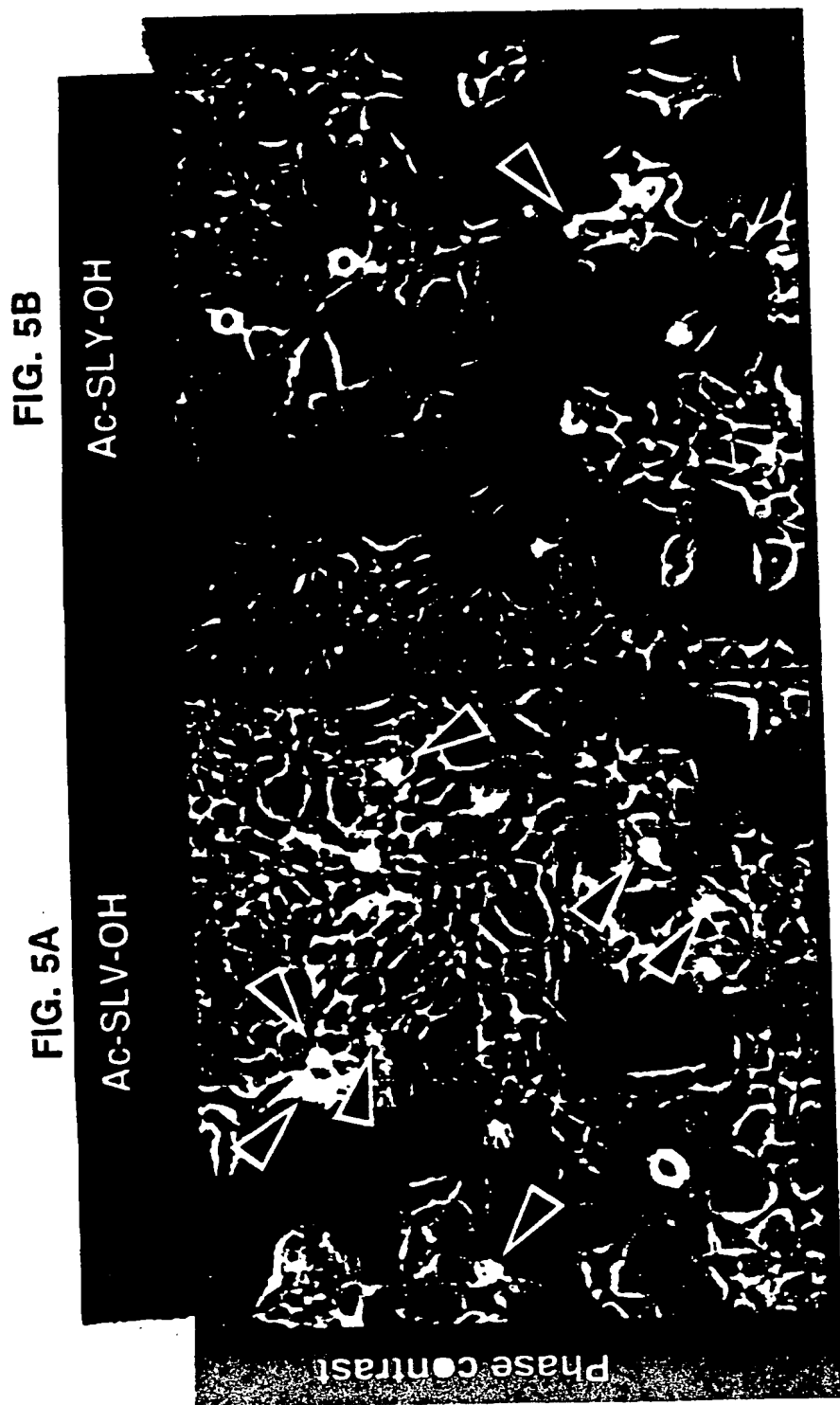
FIG. 4B



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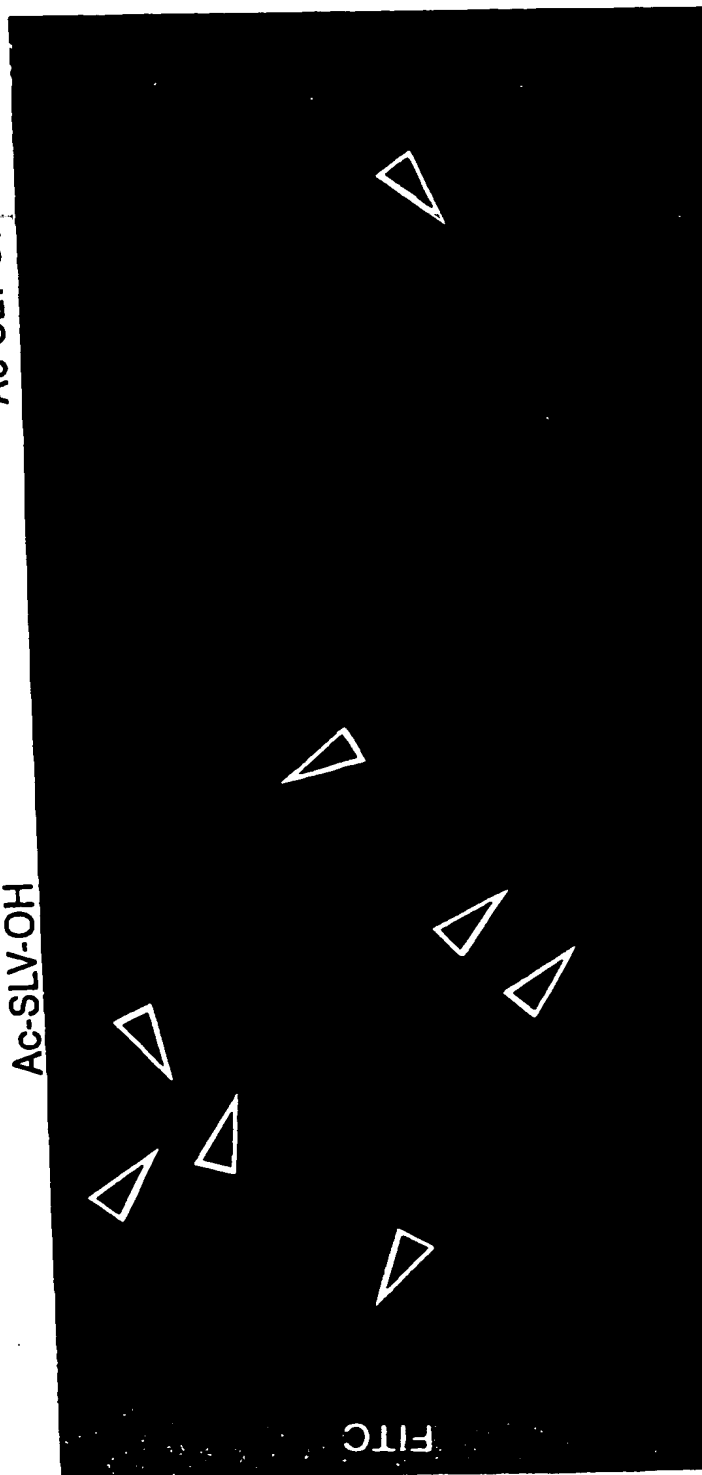
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FIG. 5D
Ac-SLY-OH

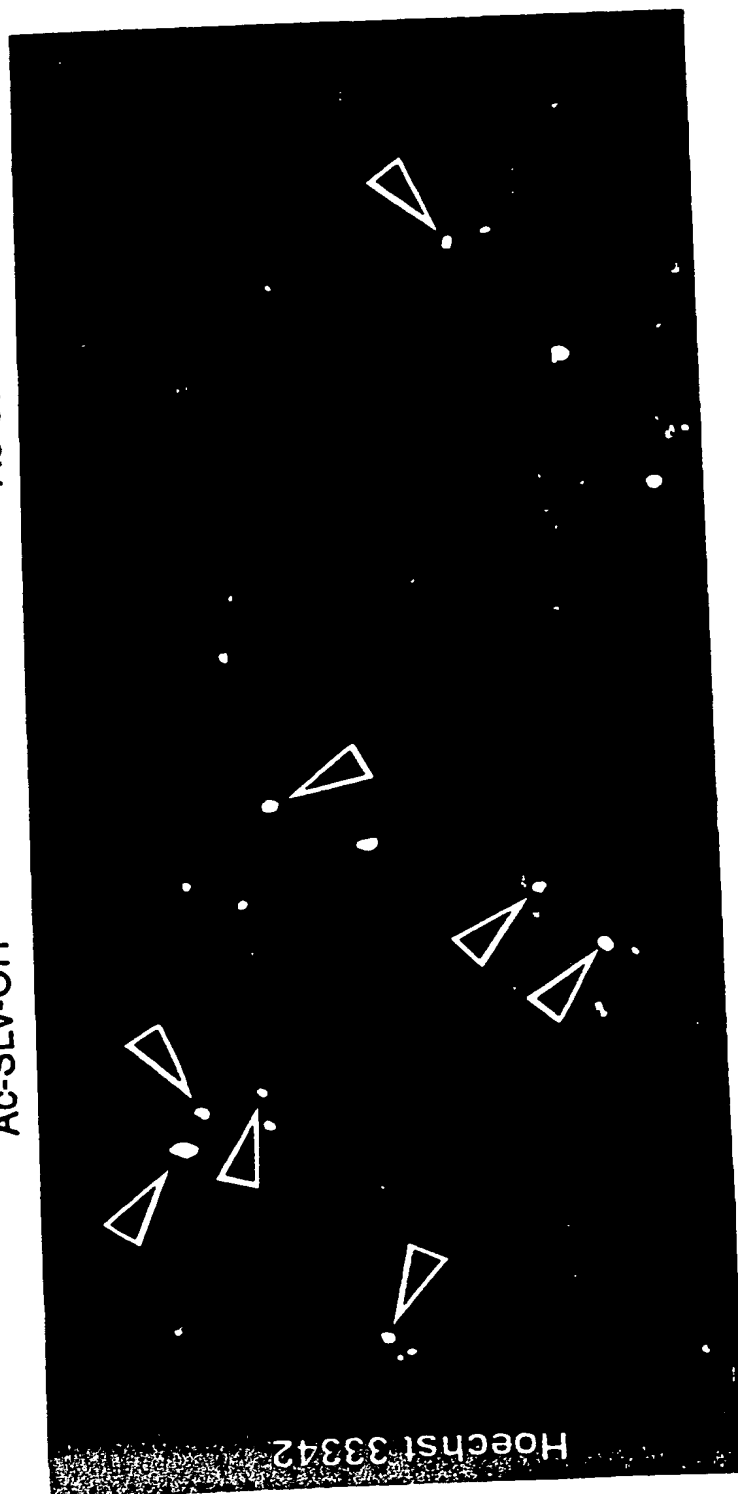
FIG. 5C
Ac-SLV-OH



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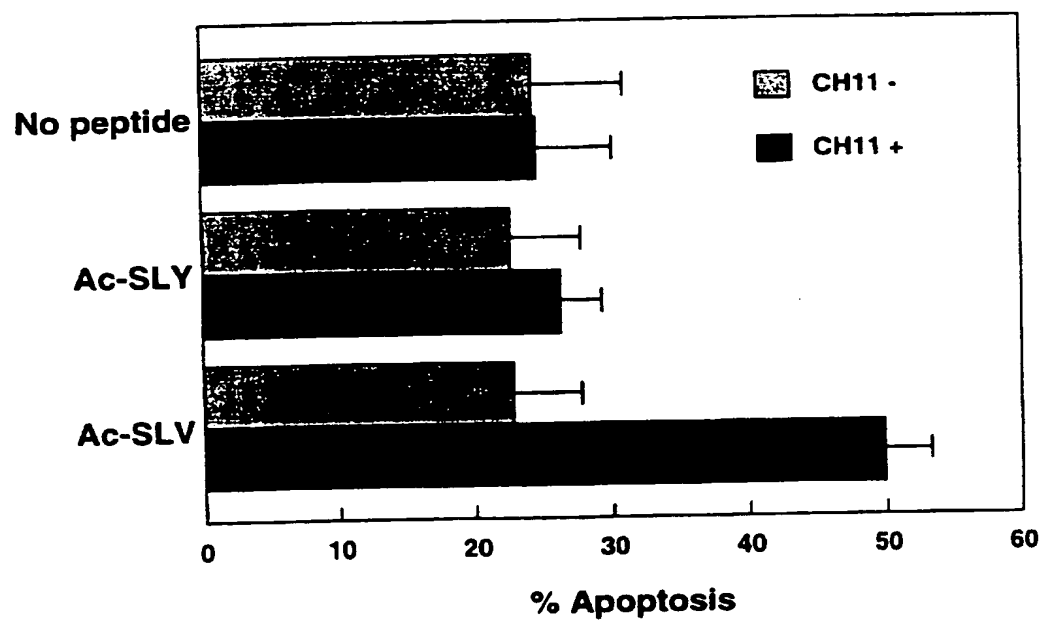
FIG. 5F
Ac-SLY-OH

FIG. 5E
Ac-SLV-OH



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FIG. 6



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FIG. 7A

NGF Rec ptor

1 mgagatgram dgprllllll lgvsllggake acptglyths gecckacnlg egvaqpcgan
 61 qtvcepclds vtfsdvvsat epckpctecv glqmsapcv eaddavcrca ygyyqdettg
 121 rceacrvicea gsglvfscqd kgntvceecp dgtysdeanh vdpclpctvc edterqlrec
 181 trwadaecee ipgrwitrst ppegdstap stqepeappe qdliastvag vvtvmgssq
 241 pvvtrgttdn lipvycsila avvglvayi afkrwnsckq nkqgansrpv nqtppegek
 301 lhsdsgisvd sqslhdqph tqtasgqalk gdgglysslp pakreevekl lngsagdtwr
 361 hlagegyqp ehidsfthea cpvrallasw atqdsatlada llaalrriqr adlveslcse
 421 statspv

FIG. 7B

CD4 Receptor

1 mnrgvpfrhl llvlqlallp aatqgkkvvl gkkgdtvelt ctasqkksiq fhwnsnqik
 61 ilgnqgsflt kgpsklndra dsrrslwdqg nfpliiknlk iedsdtyice vedqkeevql
 121 lvfgltansd thllqgslt ltlesppgss psvqcrsprg kniaggkts vsqlelqdsq
 181 twtctvlqnq kkefkidiv vlafqkassi vykkegeqve fsfplafte kltgsgelww
 241 qaerasssks witfdlknke vsvkrvtqdp klqmgkklpl hltlpqalp qagsnltla
 301 leaktgklhq evnlvmrat qlqknltece wghtspklml slklenkeak vskrekavwv
 361 lnpeagmwqc llsdsgqvl esnikvlptw stpvqpmali vlggvagl11 figlgiffcv
 421 rcrhrrrqae rmsqikrlls ekktcqcp~~hr~~ fqktcspi

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FIG. 7C

Species	C-terminal sequences of NGFR (p75)	Binding activity of FAP-1
Human	SESTATSPV-COOH	+
Rat	SESTATSPV-COOH	+
Chicken	SESTATSPV-COOH	+

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FIG. 7D

1 mnsqvamkyg ndsaaelsel hsaalaslkq divolnkrilq qtererdlle kklakaqceq
 61 ehlmhrehedv qerttllryee ritelhsvia elnkkidrlq qttireedey selrselsqs
 121 qhevmedsrs mdqdtstsvsi penqetmvtat dmdncsdins elqrvtigle nvvcgrkkss
 181 csisvaevdr hieqlttase hcdlaiktve eiegvlgrdl ypnlaeersr wekelagire
 241 enesltamlc skeeelnrtk atnnaireer drlrrrvrel qtrlqvqat gppsppgrits
 301 tnrpinpstg elstssssnd ipiakiaerv klsktrssss sdrpvlgsse issigvsssv
 361 aohiahsldq csniqeifqt lyshgsaisa skirefevet orlneriehl ksqndlltlt
 421 leecksnaer mamlvgkyoe natairlalq yseqcieaye lllalaeoeq slllgcfraa
 481 gvgsepgdqs gdenitqmlk rahdcrktae naakallmkl dgscggafav agcsvqpwee
 541 lssnshtstt sstaesscdte ftkedeqrk dyiqqlkndr aavkltmlel esihidplsy
 601 dvkprgdsqr ldlenavlmg elmankeema elkaqllylle kekalelkl streaqeqay
 661 lvhiehlkso vaeqkeqrmr slsstssgsk dkpgkecada aspalslael rttcsenela
 721 aeftnafrre kklkarvqel vsalerlts seirhqgsae fyndlkrans nlvaayekak
 781 kkhqnklikl esqmmamver hetqvmllkq rialloons rphtneal

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FIG. 7E

1 madvfpgnds tasqdvantf arkgalrqkn vhevkdhkf1 arffkqptfc shctdfiwgf
 61 gkqgfcqvc cfvvhkrche fvtfscpgad kgpdtddprs khkfkhtyg spfcfcdhcg
 121 llyglihqgm kcdtcmmvh kgcvinvp1 ipdpkneskq cgm dhtekrg riylkaevad ekltvtvrda
 181 knlipndpng lsdpyrk1kl fgvselmkmp asgwykllng eegeymvp1 pegdeegnme
 241 sveiwedart trndfngsls gpagnkvisp sedrkqpsnn ldrvkltdfn flmvlkgstf gkvmladrkg
 301 lrqkfekakl kkdvv1qdd vfectmvekr vfyaaelsig ayqpygksvd waygvllve mlagppfdg
 361 te lya1k1l kvgkfkepqa tpdya1peii glmtkbpakr lgcgpegerd vrehaffri
 421 nggdlmyhiq dgtttrtfcg lskeavslck trggpvltpg dqlvianidg sdfegfsym
 481 dfgmckeum dgtttrtfcg lskeavslck trggpvltpg dqlvianidg sdfegfsym
 541 ededelfqsi mehmvsypks kgaenfdkff
 601 dweklenrei qppfkpkvcg
 661 pqfvhpl1q1 AY

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FIG. 7F

1 mdilceents lestcnslmq inddtrlysn dfnsgeants dafnwtvdse nrtalscegc
 61 lpsclslh lqekwsall tavvlltia gnilvimavs lekklqpatn yflmslaiaad
 121 mlglflvmpv smltilygyr wplpsklcav wylldvlfst asimhlcais ldryvaigmp
 181 ihhsrfnsrt kafkliaav tsvglcmpl pvfqlqddsk vfkcgscilla ddnfvliggef
 241 vsff'pleim vityfltkis lqkeatlcvsv dlgttraklas fsflpqesls seklfgrsah
 301 repggytgrz cmqsisneqk ackvlgivff lfvmwcpff itriravick escedviga
 361 lnvfwigy lssavnpivy tlnktyrsa fsrylqcqyk enkkplqlil vnt'palayk
 421 seqlmgqkx nskqdakttd ndcsmvalgk qhseeaskdn edgvnekvay

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FIG. 7G

1 malsyrvsel qstipehiq stfvhvissn wsglqtesip eemqiveeq gnklhwaall
 61 ilmviptig gntlvllavs leklqyatr yflmelavad llvglfvmpi alltlnfeam
 121 wplplvlcpa wlfldvlfst asimhlcais vdryiaikkp iqanqynsra taf:kitvw
 181 llsiglaipv plkgfotdvd npnnitcvlt kerfgdmlf gslaafftpi alnivtyflt
 241 ihalqkkayl vknkppqrlt wltvstvqr detpcsspek vamlgdsrkd kalpnsdget
 301 lmrrestigk ksvqtieneg raskvlgivf flflmwcpf fitnltvlc dscnqttlqm
 361 lleifwigy vssgvnplvy tlfkktfrda fgryitcmvr acksvktlrk reskiyfrnp
 421 maenskfkk hgirnnginpa myqspmrirs stiqss:i: ldtllltene gdkteeqvay
 481 Y

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FIG. 7H

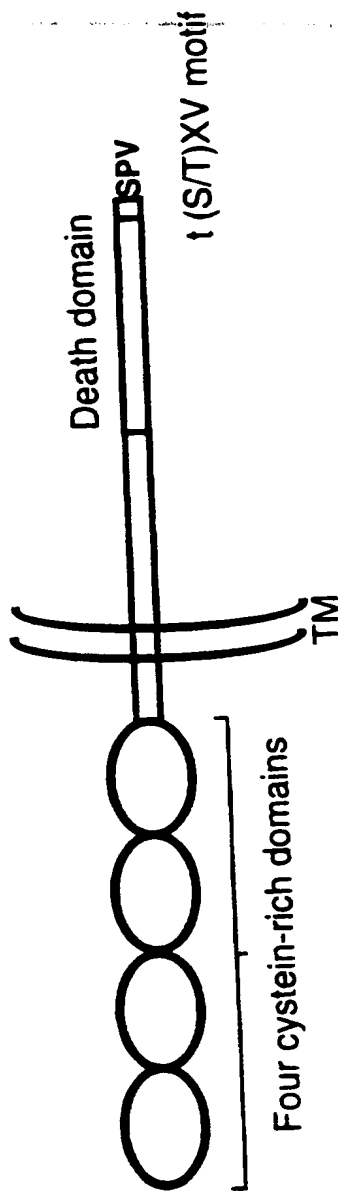
1	maaasydqil	kqvealkmen	snlrqeledn	snhltklete	asnmkevlkq	lqgsiedear
61	assgqidlle	rikelnidss	nfpqvklsrk	mslrsygere	gsvssrsgec	spvpngsfpr
121	rgfvngsres	tgyleeleke	rsllladldk	eekekdwyya	qlqnltkrid	slptanfsi
181	qtdmtrrrle	yearqirvan	eeqigtcqdm	ekraqrriar	iqqiekdlir	irqlilqsqat
241	eaerssqkxh	ezgshdaerq	negqgvgein	natsgngqgs	ttmndnetas	vlssssthsa
301	prrltshlgt	kvemvyslle	mlgthdkddm	srlliamess	qdscismrqs	gclpiliql
361	hgndkdsvli	gnsrgskear	arasaalhni	ihsqpddkrg	rreirvlhli	eqiraycetc
421	wewqeahepg	mdqdkmpmpa	pvehqicpav	cvlmklisfde	ehrhannalg	qlqaiaeliq
481	vdcmeygltn	dhysitlrry	agmaltnitf	gdvankatic	smkgcmraiv	qiksesedl
541	qqviasvlrn	lswradvnsk	ktlrevgsvk	almecalevk	kestlksvls	alwnlsahse
601	erkadicavd	galafivgtl	tyrsqntcla	iiesgggilr	nvssliatne	dhrgilrenn
661	clqtlilqlk	shsltivsna	cgtlwnlsar	npkdqealwd	mgavsmiknl	ihskh'miam
721	gsaaa'irnlm	anrpakykda	ninspgsslp	slhvrkqkal	eaeldaghlis	etfdnicnlis
781	pkashrskqr	hkqslygdv	fdtnrhddnr	sdnfnrtgrnt	vlspylnttv	lpsssssrqs
841	ldssrsekdr	slerergigl	gnyhpatenp	gtskrglqi	sttaaqlakv	neevsaihts
901	qedrssgstt	elhcvtderm	alrrssaah	hsntynftks	enrnrctcmp	yakleykrss
961	ndslnavsss	dgygkrqgm	psiesysedd	eskfcsgygy	padlahkihs	anbmddndge
1021	ldtpinyslk	ysdeqlnsgr	qspsqnerwa	rpkhlidede	kqseqrqsrn	qsttypvyte
1081	stddkhlkfq	phfgqqecvs	pyrsrgangs	etnrvgsnkg	ingnvsqslc	qeddyeddkg
1141	twyserysee	eqheeeerpt	nysikyneak	rhvddpidys	lkvatdipss	qkqsfesks
1201	ssgqsskteh	masssentst	pssnakrgnq	lhpsaqsrs	gqpqkaatck	vssingetiq
1261	tycvedtpic	fsrccslasl	ssaedeigcn	qttqeadsan	tlqiaeikek	igtrsaedpv
1321	sevpavsqhp	rtkssrlqgs	slssesarhk	avefssgaks	paksgaqtpr	sppehyvqet
1381	plmfsrctsv	ssldsfeers	lassvqsepc	sgmvsgilsp	sdldpspgqt	mppsrektpp
1441	pppqtaqtcr	evpknkapt	ekresgpkqa	avnaavqrqv	vlpdadtlil	fatestpdgf
1501	scssslsals	ldepfiqkdv	elrmpgvqe	ndngretase	qpkcsnenge	kaaektidse
1561	kdildddddd	dieileecil	samptkssrk	akkpqaatask	lpppvarkps	qlpvylkls
1621	qarlqppkhv	sftpgdamp	vycvegtpin	fstatslsdl	tiesppnela	agegvrsgaq
1681	sgfekrditi	ptegrstdea	qsgktsavti	peldnkaee	gdilaecins	ampkgkshkp
1741	frvkkimdv	qqasasssap	nknqldgkkk	kptspvkip	qnteyrtrvr	knadsknnln
1801	aervfsdnkd	sktknlnkns	kdfndklpn	edrvggsfaf	dspthypie	gtpycfsrmd
1861	slssldfddd	dvdlsrekae	lrkakankes	eakvtshte	tsnqqsankt	qalakkpinr
1921	gqpkpilqkq	stfpqsskdi	pdrgaatdek	lqnfaientp	vcfshnssls	slsdidqenn
1981	nkenepiket	eppdsqggs	kpqasgyapk	sfhvcdtpvc	fsmssslssi	sidseddlq
2041	ecissampkk	kcpserlkgn	ekhsprnmgy	ilgedltidi	kdiqrpdseh	glspdsenfd
2101	wkaiqegans	lvsslhqaaa	aacslrqass	dsdsilslks	gislgspfh	tpdqeekqft
2161	snkgppriikp	gekstletkk	ieseskgikg	gkkvykslit	gkvrnsneis	gqmkqplqan
2221	mpsisrgtrm	ihipgvtrns	sstspvskkg	pplktpasks	psegqtatts	prgakpsvks
2281	elapvarqts	qiggsskaps	rsqsrdstps	rpaaqpalsr	iqspgrnsis	pgrngisppn
2341	klsqprts	petastkssg	sgkmsytspg	rqmsqqultk	qtgisknass	iprsesaskg
2401	lnqmnngnga	akkvelsrms	stkssgsesd	rserpvlvrq	stfikeapsp	tlrrkleesa
2461	efeslspssr	pasptrsqaq	tpvlspslpd	mslsthassv	aggrwkllpn	leptieyndg
2521	rpakrhdiar	shsespsrlp	inrsgtwkre	hskhssslpr	vstwrtrgss	silssasses
2581	sekaksedek	hvnslsgtkq	skengvsakg	twrkikenef	spntnstqtv	ssgatngaes
2641	ktliygmapa	vsktedvvr	iedcpinapr	sgreptgntp	rvidsvseka	npnikdskdn
2701	qaknvgngs	vpmrtvglen	rlnsfiqvda	pdqkgteikp	gqnnpvpvse	tnessivert
2761	pfssassskh	aspsqtvaar	vtpfnynpnp	rkssadstsa	rpsqiptpvn	nntkkrdskt
2821	dstassgtqs	pkrhsgsylv	END			

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FIG. 8

p75NGFR

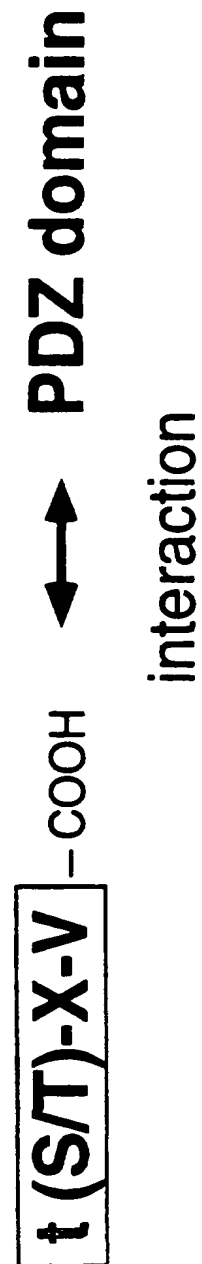
(Low-affinity nerve growth factor receptor)



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FIG. 9

	C-terminal amino acid sequence
Fas	NEIQSLV
p75NGFR	STATSPV



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FIG. 10
In vitro interaction of ³⁵S-labeled FAP-1 with various receptors
— FAP-1 binds to the cytoplasmic region of p75NGFR. —

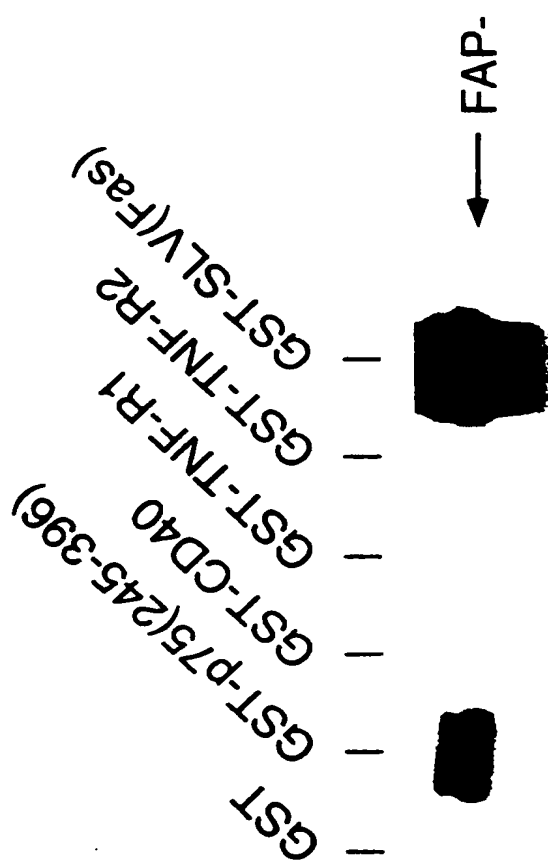
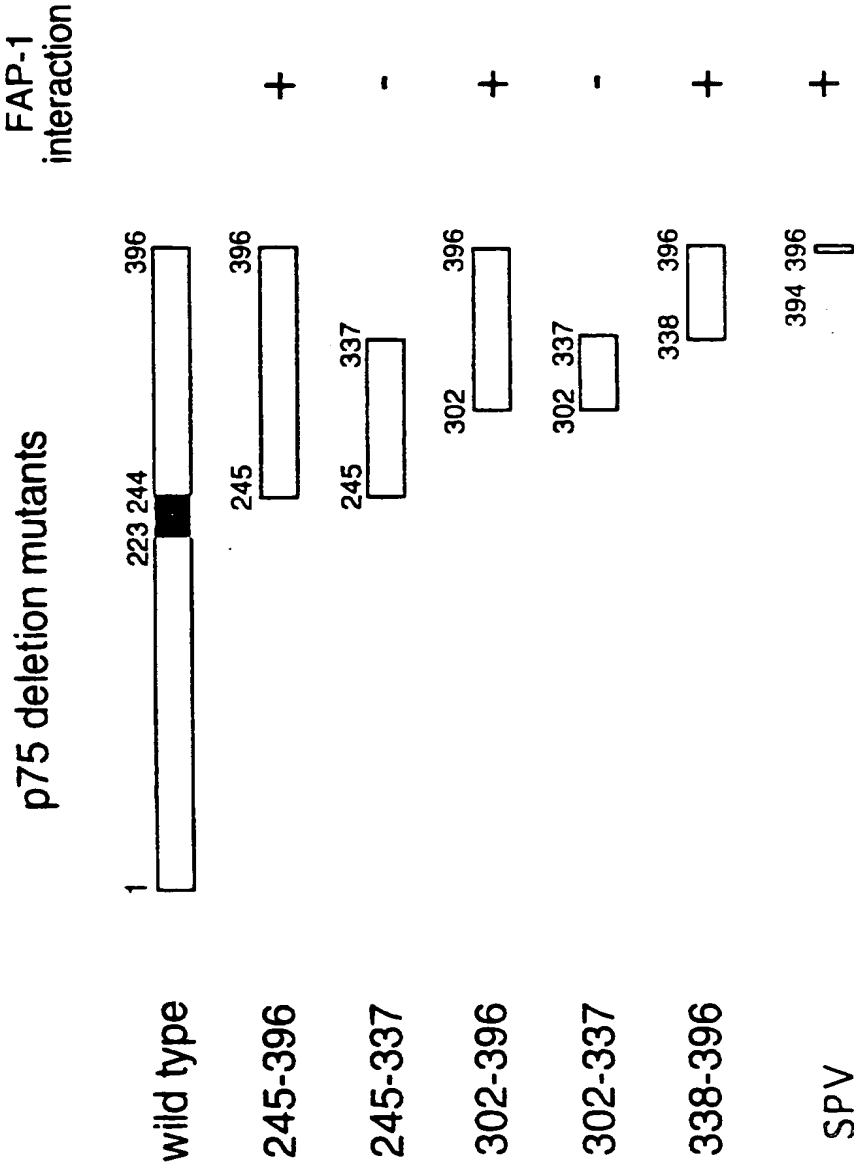


FIG. 11A
FAP-1 binds to C-terminal three amino acids SPV of p75NGFR.



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FIG. 11B

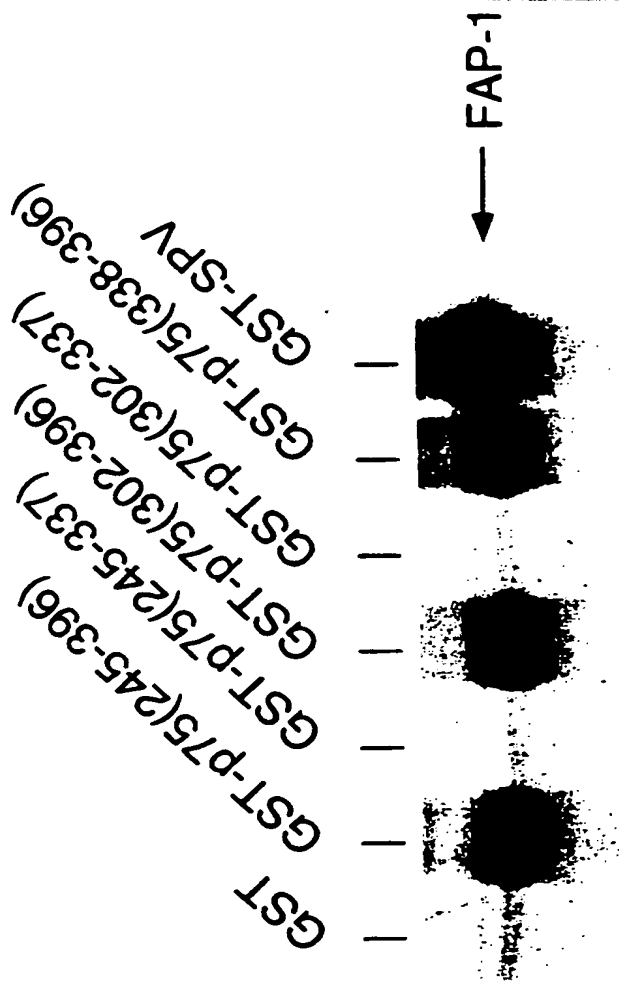


FIG. 12

FAP-1 binds to p75NGFR C-terminal cytoplasmic region in yeast.

VP16-FAP-1 VP16-cRaf

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LexA-p75NGFR(338-396)

+

-

LexA-p75NGFR(365-396)

+

-

LexA-Fas

++

-

LexA-Ras^{V12}

-

+

LexA-Lamin

-

-

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/12677

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : Please See Extra Sheet
US CL : 424/198.1; 514/2; 530/351; 435/7.1, 7.23
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/198.1; 514/2; 530/351; 435/7.1, 7.23

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS, DIALOG

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	DOYLE. D.A. et al. "Crystal Structures of a Complexed and Peptide-Free Membrane Protein-Binding Domain: Molecular Basis of Peptide Recognition by PDZ." Cell. June 1996. Vol. 85. pages 1067-1076, especially page 1067.	1-120
Y	MATSUMINE. A. et al. "Binding of APC to the Human Homolog of the Drosophila Discs Large Tumor Suppressor Protein." Science. May 1996. Vol. 272. No. 5264. pages 1020-1023, especially page 1020.	1-120
Y	KORNAU. H.-C. et al. "Domain Interaction Between NMDA Receptor Subunits and the Postsynaptic Density Protein PSD-95." Science. September 1995. Vol. 269. No. 5231. pages 1737-1740, especially page 1737.	1-120



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
A document defining the general state of the art which is not considered to be of particular relevance	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
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Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

Facsimile No. (703) 305-3230

Authorized officer

YVONNE E. LARSEN

Telephone No. (703) 308-0196

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/12677

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y,P	US 5,632,994 A (REED et al) 27 May 1997, col. 2, lines 12-56.	1-120
Y	WO 96/18641 A1 (YEDA RESEARCH AND DEVELOPMENT CO. LTD.) 20 June 1996. pages 1-57, especially page 6	1-120
Y	ZHANG, J. et al. "A Mouse Fas-Associated Protein with Homology to the Human MORT1/FADD Protein is Essential for Fas-Induced Apoptosis." Molecular and Cellular Biology. June 1996. Vol. 16. No. 6. pages 2756-2763, especially page 2756.	1-120

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US97/12677

A. CLASSIFICATION OF SUBJECT MATTER:

IPC (6):

A61K 38/00, 39/00; C07K 1/00, 14/00, 17/00; G01N 33/53, 33/567, 33/574